A Multicenter, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in the Treatment of Subjects With Amyotrophic Lateral Sclerosis (ALS)

Mallinckrodt Pharmaceuticals

Background

- ALS, a neurodegenerative disorder that affects the upper and lower motor neurons in the central nervous system, causes death in up to 70% to 80% of patients within 5 years of symptom onset[1]
- More than 30 agents have shown promise in preclinical and in vitro ALS models but have failed to modify the disease in humans[2,3]
- Acthar may have neuroprotective, neuroregenerative, and anti-inflammatory effects that could potentially delay or halt the progression of ALS
- In a pilot study, post hoc analyses suggested that Acthar may delay disease progression, as assessed by the ALS Functional Rating Scale over time; Acthar was well tolerated, and there were no unexpected TEAEs

Purpose

- The purpose of this study is to examine the effect of Acthar on ALS progression



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ALS is a neurodegenerative disorder that affects the upper and lower motor neurons in the central nervous system.

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Objectives

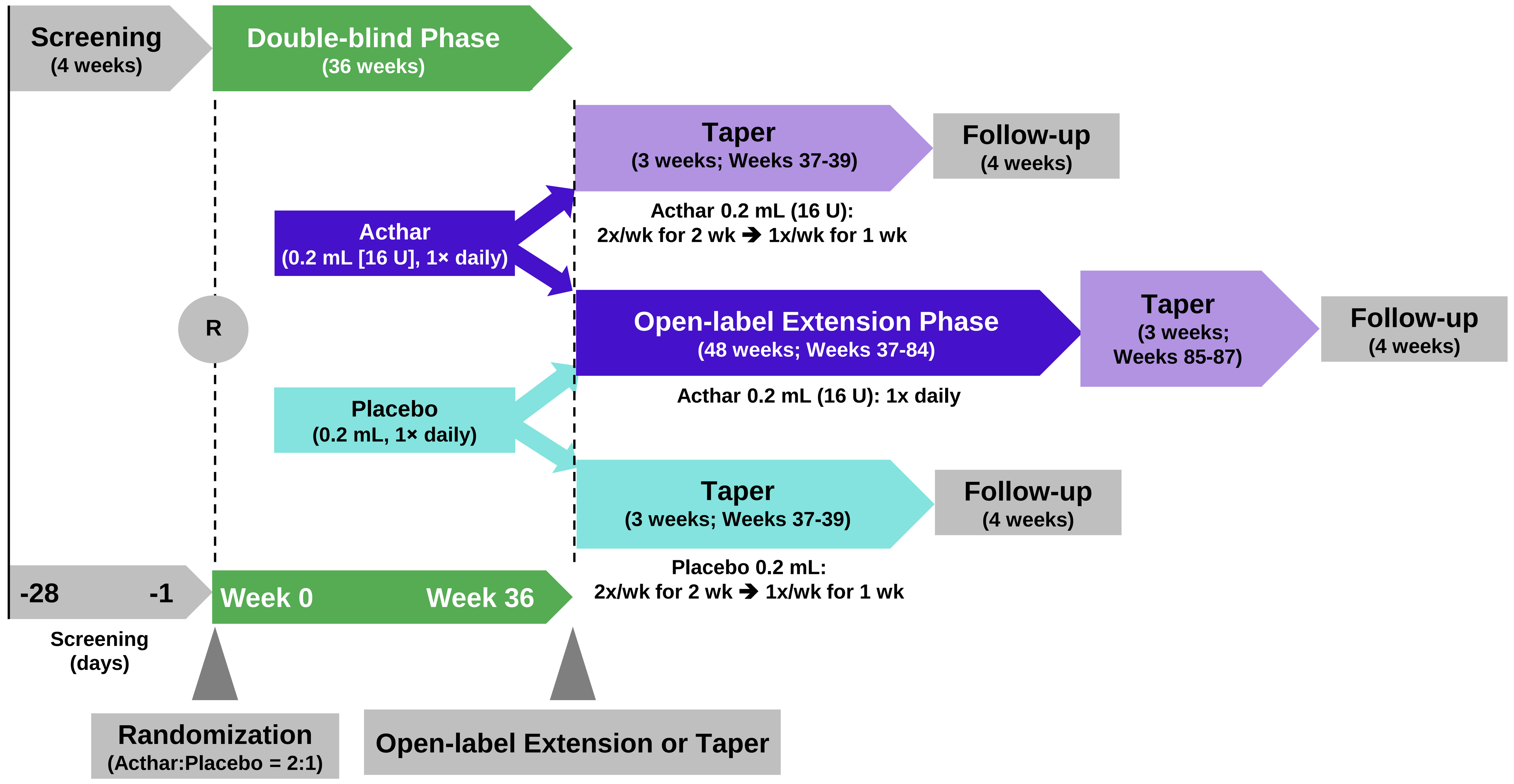
- The primary objective of this study is to assess the effect of Acthar (given once daily as a 0.2-mL [16-U] dose for 36 weeks) on functional decline using the ALSFRS-R
- Secondary objectives are to assess the safety and tolerability of Acthar, its effect on survival, and its longitudinal effects on functional decline and survival in subjects with ALS

Study Population

- Males or females
- 18 to 75 years of age
- Diagnosis of ALS (clinically definite, clinically probable-laboratory supported, clinically probable) per
 - Revised El Escorial criteria
 - Onset of symptoms (first muscle weakness or dysarthria) ≤2 years prior to Screening Visit
- Predicted FVC ≥60%
- Blood pressure ≤140/90 mm Hg
- Exclusion of edaravone (2-week washout prior to randomization)
- If receiving riluzole, maintenance of stable dose for 4 weeks
- No history of type 1 or 2 diabetes

Study Design

- Anticipated enrollment: ~213 subjects



Screening
(4 weeks)
Double-blind Phase
(36 weeks)
Taper
(3 weeks; Weeks 37-39)
Follow-up
(4 weeks)
Acthar 0.2 mL (16 U):
2x/wk for 2 wk ➔ 1x/wk for 1 wk
Acthar
(0.2 mL [16 U], 1× daily)
R
Open-label Extension Phase
(48 weeks; Weeks 37-84)
Acthar 0.2 mL (16 U): 1x daily
Taper
(3 weeks;
Weeks 85-87)
Follow-up
(4 weeks)
Placebo
(0.2 mL, 1× daily)
Taper
(3 weeks; Weeks 37-39)
Follow-up
(4 weeks)
Placebo 0.2 mL:
2x/wk for 2 wk ➔ 1x/wk for 1 wk
-28
-1
Screening
(days)
Week 0
Week 36
Randomization
(Acthar:Placebo = 2:1)
Open-label Extension or Taper

Study Endpoints

Primary Endpoint

- Change from baseline in the telephone-administered ALSFRS-R total score at Week 36

Key Secondary Endpoints

- Mean slope of ALSFRS-R total score decline
- Change from baseline in ALSFRS-R total score over time
- Mean slope of decline in pulmonary test scores (FVC, FEV_1, and SVC)
- Survival
- Summary of general safety profile, including AEs (serious and nonserious), vital signs, and laboratory assessments, by study period and over the entire study

References

1. Beghi E, Logroscino G, Chiò A, et al. The epidemiology of ALS and the role of population-based registries. *Biochim Biophys Acta.* 2006;1762(11-12):1150-1157.
2. Aggarwal S and Cudkowicz M. ALS drug development: reflections from the past and a way forward. *Neurotherapeutics.* 2008;5(4):516-527.
3. Gordon PH and Meininger V. How can we improve clinical trials in amyotrophic lateral sclerosis? *Nat Rev Neurol*. 2011;7(11):650-654.

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Abbreviations: AE, adverse event; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; FEV_1, forced volume expired in 1 second; FVC, forced vital capacity; SVC, slow vital capacity; TEAE, treatment-emergent adverse event.

Post Hoc Analyses Using the PRO-ACT Database to Evaluate Repository Corticotropin Injection (H.P. Acthar® Gel) as a Potential Treatment for ALS

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Introduction

- Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that results in progressive muscle paralysis and disability; eventual mortality often occurs within 5 years of symptom onset and is most commonly caused by respiratory failure[1,2]
- Riluzole and edaravone are the only agents currently approved by the FDA for the treatment of ALS[3,4]
 - Riluzole has shown only modest effects on survival, prolonging survival by an average of 2 to 3 months[5]
 - The effects of edaravone on delaying functional decline were demonstrated in patients with early disease defined by time from symptom onset, functional decline, and respiratory function[6]
- Although more than 30 other agents targeting different ALS pathways have shown promise in preclinical models, few have demonstrated clear benefit in clinical trials[4,5]
- Repository corticotropin injection (RCI; H.P. Acthar Gel; Mallinckrodt ARD, Inc., Bedminster, NJ, USA) is a naturally derived product that contains a highly purified porcine analogue of adrenocorticotropic hormone (ACTH)
- ACTH has been shown to activate all 5 known melanocortin receptors (MCR1-5), and MCR expression has been demonstrated on ALS-relevant tissues, including the cerebral cortex, spinal cord, and muscles[7]
 - Its anti-inflammatory effects may be mediated by the downregulation of pro-inflammatory cytokines and chemokines and the attenuation of inducible nitric oxide synthase and nitric oxide via MCR receptors[8,9]
 - ACTH may also have neuroprotective and neuroregenerative effects that could slow the progression of motor neuron death[7,10]
- Findings from a previous open-label pilot study (ClinicalTrials.gov identifier: NCT01906658) demonstrated that RCI was well tolerated in 43 patients with ALS; no unexpected adverse events were observed
 - This pilot study was designed to examine the acute safety and tolerability of 4 RCI dosing regimens and to inform dose selection for future ALS studies
 - Exploratory efficacy assessments included the commonly used ALS Functional Rating Scale – Revised (ALSFRS-R); both the original ALS Functional Rating Scale (ALSFRS) and the ALSFRS-R use the decline in physical function that characterizes ALS as a marker for disease severity and progression[11]
- Here, we report results from post hoc exploratory analyses of efficacy data collected during the pilot study to evaluate the potential effectiveness of RCI for the treatment of ALS

Study Objective

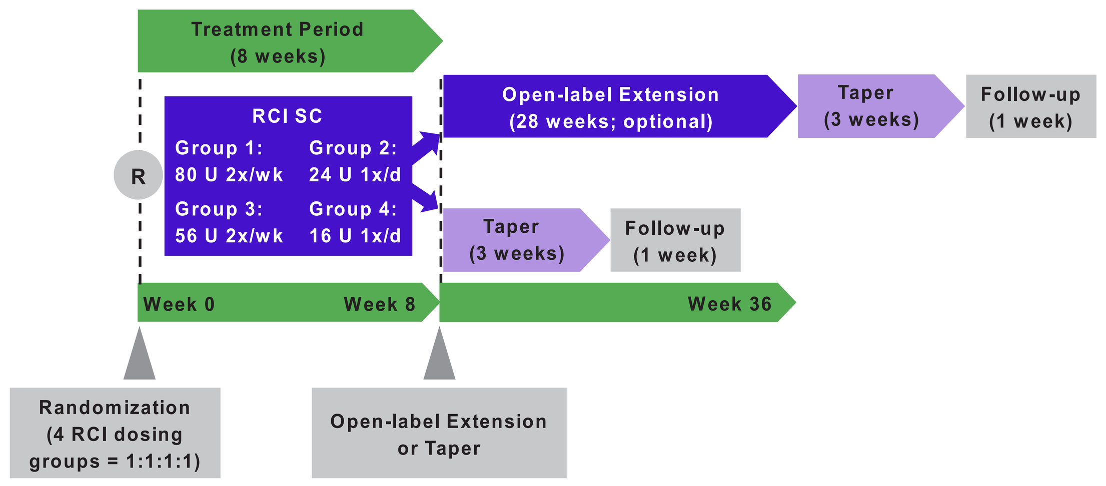
- We used data from the RCI pilot study and the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database (https://nctu.partners.org/ProACT)[12] to evaluate the potential effects of RCI on functional disease progression as measured by the ALSFRS in 2 post hoc analyses:
 - A matched case-control analysis, with historical controls derived from patients in the PRO-ACT database who received placebo
 - A slope analysis of actual ALS progression derived from the study and predicted ALS progression based on an award-winning algorithm[13] developed using PRO-ACT data

Methods

RCI Pilot Study in ALS

- This open-label pilot study evaluated 43 patients with ALS who were randomly assigned to receive 1 of 4 RCI dosing regimens (Figure 1)
- At screening, patients were categorized by 1 of 4 ALS diagnoses according to the revised El Escorial criteria:
 - Clinically definite ALS
 - Clinically probable (laboratory-supported) ALS
 - Clinically probable ALS
 - Clinically possible ALS
- Patients had ALS symptom onset within the last 3 years and an upright slow vital capacity ≥60% of predicted
- Prior to both post hoc analyses, data from all 4 RCI dosing groups in the pilot study were combined into a single RCI group, and ALSFRS-R scores collected during the study were converted to ALSFRS scores by excluding the 2 questions assessing respiration to match the PRO-ACT data

Figure 1. Pilot Study Design


Treatment Period
(8 weeks)
RCI SC
Group 1:
80 U 2x/wk
Group 2:
24 U 1x/d
Group 3:
56 U 2x/wk
Group 4:
16 U 1x/d
R
Open-label Extension
(28 weeks; optional)
Taper
(3 weeks)
Follow-up
(1 week)
Taper
(3 weeks)
Follow-up
(1 week)
Week 0
Week 8
Week 36
Randomization
(4 RCI dosing
groups = 1:1:1:1)
Open-label Extension
or Taper

Abbreviations: R, randomization; RCI, repository corticotropin injection; SC, subcutaneous.

Matched Case-Control Analysis

- Historical controls were obtained from the placebo groups of 16 phase 2 and 3 studies (n≥80 each) conducted between 1990 and 2010 and 1 large observational study (n=8635) in PRO-ACT
- A review of available literature was used to identify 7 variables associated with disease progression:
 1. ALSFRS total score
 2. Time from symptom onset to enrollment (≥18 months; <18 months)
 3. Gender (male; female)
 4. Age at symptom onset (≥40 years; <40 years)
 5. Site of onset (limb; bulbar; limb and bulbar)
 6. Body mass index (≥18.5 kg/m^2; <18.5 kg/m^2)
 7. Baseline creatinine level (≥53.04 μmol/L; <53.04 μmol/L)
- Patients treated with RCI in the study were matched with up to 3 PRO-ACT controls using all identified variables
- Mean changes in ALSFRS total score from baseline at weeks 8 and 36 were compared among the RCI and control groups using a linear mixed-effects model with repeated measures, with treatment, time, and treatment-by-time interaction as fixed effects; baseline ALSFRS total score was adjusted in the mixed-effects model
- p-values <0.05 were considered statistically significant

PRO-ACT Prediction Algorithm Analysis

- The actual observed slope for ALS progression after 36 weeks of RCI treatment in the pilot study was calculated as follows:

$$\frac{\text{(ALSFRS [week 36] – ALSFRS [baseline])}}{\textit{(month [week 36 visit – baseline visit])}}$$

- We adapted an award-winning algorithm from the DREAM Phil Bowen ALS Prize4Life Challenge[13] that was developed using PRO-ACT data to derive a predicted slope for ALS progression at week 36 using 50 baseline features including patient demographics, disease characteristics, treatment, and laboratory test results
 - The algorithm was modified to use random forests and only the features that were available from the pilot study
 - The modified algorithm was cross-validated using a subset of PRO-ACT data, with the root mean square error of the modified algorithm (0.517) demonstrating a better performance than that of the original algorithm (0.559)
- Mean values of the actual observed and PRO-ACT algorithm−predicted slopes for the 21 patients who completed the pilot study through week 36 were compared using a 2-sided paired *t* test
- p-values <0.05 were considered statistically significant

Results

Matched Case-Control Analysis

- The 43 cases from the pilot study were matched with 106 PRO-ACT controls; no significant differences in any matching variables were seen between groups (Table 1)

Table 1. Baseline Characteristics of Patients From the Pilot Study and Matched PRO-ACT Controls

Characteristic	Statistic/ Category	Pilot Study (RCI; n=43)	Matched PRO-ACT Controls (placebo; n=106)	p-Value[a]
ALSFRS total score	Median (IQR)	28.0 (8)	28.0 (9)	0.60
Time from symptom onset	<18 months	21 (49)	45 (42)	0.48
	≥18 months	22 (51)	61 (58)	
Gender	Male	26 (60)	71 (67)	0.45
	Female	17 (40)	35 (33)	
Age at symptom onset	<40 years	5 (12)	11 (10)	0.82
	≥40 years	38 (88)	95 (90)	
Site of onset	Limb	33 (77)	85 (80)	0.64
	Bulbar	10 (23)	21 (20)	
BMI	<18.5 kg/m^2	0	1 (1)	0.53
	≥18.5 kg/m^2	41 (100)	105 (99)	
Creatinine level	<53.04 μmol/L	16 (37)	24 (23)	0.07
	≥53.04 μmol/L	27 (63)	83 (77)	

Abbreviations: ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; BMI, body mass index; IQR, interquartile range; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials; RCI, repository corticotropin injection.
Data are No. (%) of patients unless otherwise indicated.
[a] p-Values are from the Wilcoxon rank sum test or chi-square test; values <0.05 were considered statistically significant.

- Mean ALSFRS total scores were higher in RCI-treated patients from the pilot study than in PRO-ACT placebo-treated controls at both week 8 and week 36 (Table 2)
 - The least-squares mean score changed significantly less from baseline in RCI-treated patients than in placebo-treated controls at week 36

Table 2. Longitudinal Data Analysis Results for Change From Baseline in ALSFRS Total Score

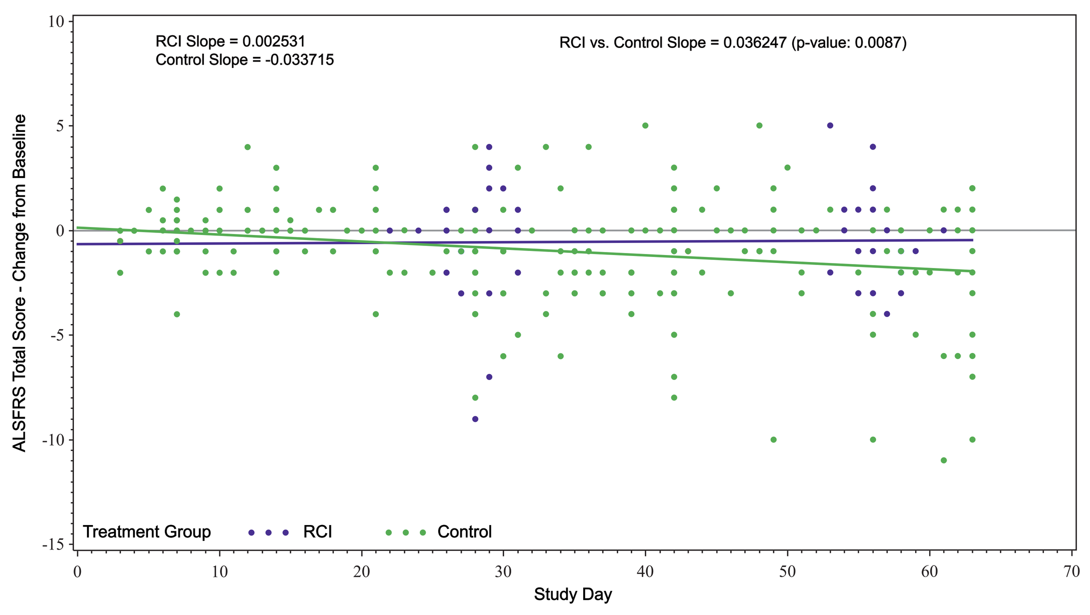
Time Point	Statistic	Pilot Study (RCI; n=43)	Matched PRO-ACT Controls[a] (placebo; n=106)
Baseline	n	43	106
	Mean±SD	**27.8±5.55**	**27.2±6.31**
	Median	28.0	28.0
	Range	(16.0, 37.0)	(13.0, 37.0)
Week 8	n	37	53
	Mean±SD	**28.0±5.41**	**26.5±7.42**
	Median	28.0	28.0
	Range	(13.0, 37.0)	(12.0, 38.0)
Change from baseline at week 8	Mean±SD	−0.4±1.88	−2.0±3.32
	LS mean±SE	−0.5±0.32	−0.9±0.20
	LS Mean difference±SE	0.4±0.38	
	95% CI	−0.4, 1.1	
	p-Value	0.327	
Week 36	n	21	89
	Mean±SD	**24.1±8.11**	**20.9±9.10**
	Median	25.0	22.0
	Range	(7.0, 36.0)	(1.0, 38.0)
Change from baseline at week 36	Mean±SD	−4.3±4.71	−6.6±5.57
	LS Mean±SE	−2.2±0.55	−3.6±0.32
	LS Mean difference±SE	1.4±0.64	
	95% CI	0.2, 2.7	
	p-Value	0.025	

Abbreviations: ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; CI, confidence interval; LS, least squares; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials; RCI, repository corticotropin injection; SD, standard deviation; SE, standard error. [a] The PRO-ACT control group is treated as the reference group.

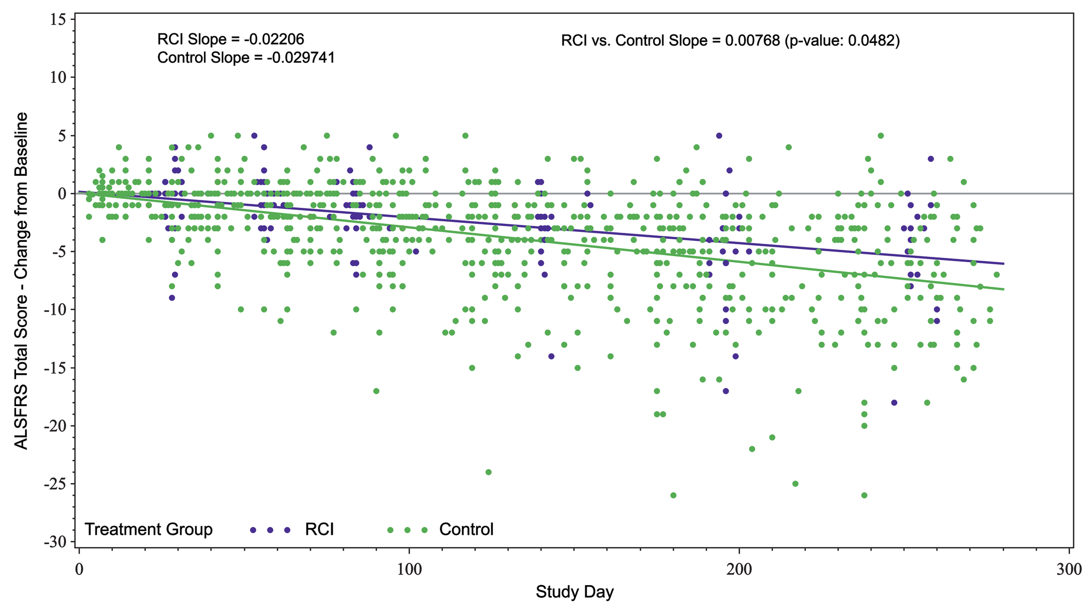
- Slope estimates for weeks 8 and 36 also demonstrated that there was significantly less of a decline in ALSFRS total score in RCI-treated patients than in placebo-treated controls (Figure 2)
 - Week 8 slopes: RCI, 0.003; placebo, −0.034 (slope difference, 0.036 [95% CI: 0.009, 0.063]; p=0.009; Figure 2A)
 - Week 36 slopes: RCI, −0.022; placebo, −0.030 (slope difference, 0.008 [95% CI: 0.000, 0.015]; p=0.048; Figure 2B)

Figure 2. Slope Estimates for Change From Baseline in ALSFRS Total Score

A. Week 8[a]


RCI Slope = 0.002531
Control Slope = -0.033715
RCI vs. Control Slope = 0.036247 (p-value: 0.0087)
ALSFRS Total Score - Change from Baseline
10
5
0
-5
-10
-15
Treatment Group
RCI
Control
0
10
20
30
40
50
60
70
Study Day

B. Week 36[a]


RCI Slope = -0.02206
Control Slope = -0.029741
RCI vs. Control Slope = 0.00768 (p-value: 0.0482)
ALSFRS Total Score - Change from Baseline
15
10
5
0
-5
-10
-15
-20
-25
-30
Treatment Group
RCI
Control
0
100
200
300
Study Day

Abbreviations: ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials.
[a] The PRO-ACT control group is treated as the reference group. The intercepts of regression lines are based on the average baseline ALSFRS total score.

PRO-ACT Prediction Algorithm Analysis

- The actual 9-month rate of ALSFRS decline was slower than the predicted rate (Table 3)

Table 3. Comparison of Actual Observed and Predicted Slopes of 9-Month ALSFRS Total Score Decline

Parameter	Statistic	Actual	Predicted	P-Value
		Pilot Study (n=21)	PRO-ACT Algorithm (n=21)	
Baseline	Mean±SD	−0.51±0.57	−0.75±0.26	0.087
	Median	−0.36	−0.79	
	Range	(−2.21, 0.35)	(−1.20, −0.29)	

Abbreviations: ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; PRO-ACT, Pooled Resource Open-Access Amyotrophic Lateral Sclerosis Clinical Trials; SD, standard deviation.

Summary and Conclusions

- We conducted a post hoc matched case-control analysis using historical placebo-treated controls from the PRO-ACT database and a second post hoc analysis using an award-winning prediction algorithm for ALS progression based on PRO-ACT data
- Patients who received RCI in the pilot study had a significantly slower decline in ALSFRS total score than matched PRO-ACT placebo-treated controls
- The actual observed slope of ALSFRS total score in the patients from the pilot study declined at a slower rate than predicted by the PRO-ACT algorithm
- Findings from these 2 post hoc exploratory analyses suggest the potential for RCI to slow the rate of functional decline in patients with ALS
- These findings provide a rationale for the ongoing larger controlled study of RCI efficacy in the treatment of ALS (ClinicalTrials.gov identifier: NCT03068754)

References

1. Andersen PM, Borasio GD, Dengler R, et al. EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. *Eur J Neurol.* 2005;12(12):921-938.
2. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2009;73(15):1227-1233.
3. US Food and Drug Administration. FDA Approves Drug to Treat ALS. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm557102.htm. Published May 5, 2017. Accessed September 13, 2017.
4. Berry JD, Cudkowicz ME. New considerations in the design of clinical trials for amyotrophic lateral sclerosis. *Clin Investig (Lond).* 2011;1(10):1375-1389.
5. Aggarwal S, Cudkowicz M. ALS drug development: reflections from the past and a way forward. *Neurotherapeutics.* 2008;5(4):516-527.
6. The Writing Group; on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2017;16(7):505-512.
7. Starowicz K, Przewlocka B. The role of melanocortins and their receptors in inflammatory processes, nerve regeneration and nociception. *Life Sci.* 2003;73(7):823-847.
8. Ahmed TJ, Montero-Melendez T, Perretti M, Pitzalis C. Curbing inflammation through endogenous pathways: focus on melanocortin peptides. *Int J Inflam.* 2013;2013:985815.
9. Caruso C, Carniglia L, Durand D, Scimonelli TN, Lasaga M. Astrocytes: new targets of melanocortin 4 receptor actions. *J Mol Endocrinol.* 2013;51(2):R33-R50.
10. Strand FL, Kung TT. ACTH accelerates recovery of neuromuscular function following crushing of peripheral nerve. *Peptides.* 1980;1(2):135-138.
11. Bakker LA, Schroder CD, van Es MA, Westers P, Visser-Meily JMA, van den Berg LH. Assessment of the factorial validity and reliability of the ALSFRS-R: a revision of its measurement model. J Neurol. 2017;264(7):1413-1420.
12. Neurological Clinical Research Institute (NCRI) at Massachusetts General Hospital. PRO-ACT. https://nctu.partners.org/ProACT. Accessed September 12, 2017.
13. Küffner R, Zach N, Norel R, et al. Crowdsourced analysis of clinical trial data to predict amyotrophic lateral sclerosis progression. *Nat Biotechnol.* 2015;33(1):51-57.

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H.P. Acthar® gel is not currently FDA approved for the treatment of ALS

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Treatment of Proteinuria Due to Treatment-Resistant or Treatment-Intolerant Idiopathic Focal Segmental Glomerulosclerosis (FSGS): A 2-Part Prospective Study of H.P. Acthar® Gel (PODOCYTE)

Mallinckrodt Pharmaceuticals

Background

- Primary FSGS is a major cause of idiopathic nephrotic syndrome and is the most common primary glomerular disorder causing end-stage renal disease in the United States[1]
- Primary FSGS is a progressive disorder; ~50% of affected patients develop end-stage renal disease over a period of 5 to 8 years[2]
- Current treatments for primary FSGS are effective in <50% of patients and are associated with significant side effects[3,4]
- Acthar is approved to induce a diuresis or remission of proteinuria in nephrotic syndrome without uremia, the idiopathic type, or that due to lupus erythematosus
- Remission of proteinuria (complete or partial) in FSGS is associated with an improved renal survival rate[5]
- Data from a recently published case series suggested that 29% of patients with steroid-resistant or steroid-dependent primary FSGS achieved complete or partial remission of proteinuria after treatment with Acthar[6]

Purpose

- The purpose of this study is to provide nephrologists with additional clinical evidence regarding the efficacy and safety of Acthar in subjects with treatment-resistant or treatment-intolerant FSGS

Objectives

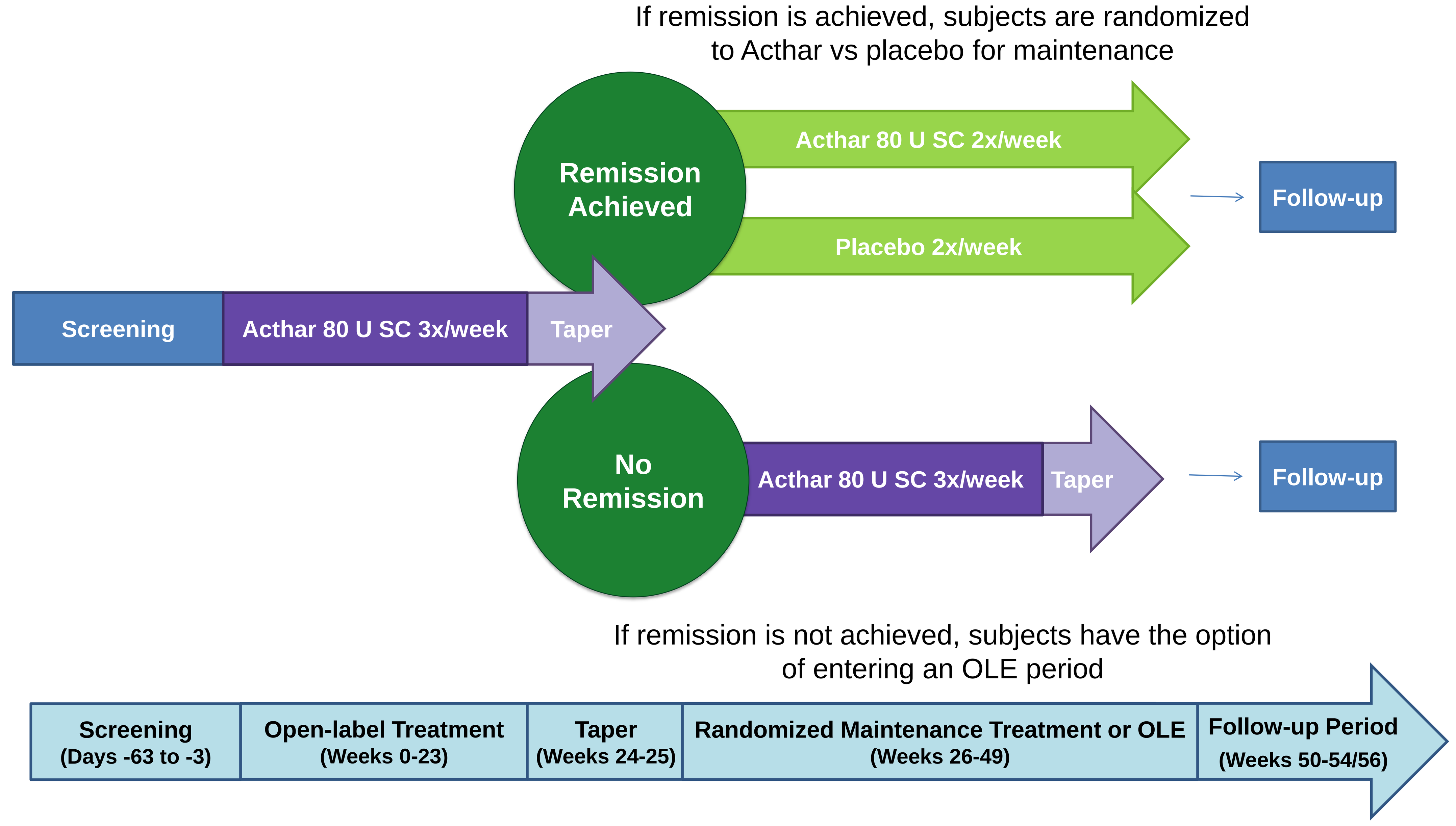
- The primary objective of this study is to confirm the efficacy of Acthar in inducing remission of proteinuria in subjects with primary FSGS who are resistant to, or intolerant of, at least 1 previous immunosuppressive therapy such as corticosteroids or CNIs
- Secondary objectives are to confirm the safety and tolerability of Acthar and to evaluate its efficacy in maintaining remission of proteinuria

Study Population

- Adult subjects (≥18 years old)
- Primary FSGS diagnosis confirmed by renal biopsy
- Nephrotic
 - uPCR >3.0 mg/mg
 - eGFR >30 mL/min/1.73m^2
- Intolerance to or failure to achieve complete or partial remission with ≥1 previous immunosuppressant
- Treatment with an ACEi/ARB ≥4 weeks before Screening
- Blood pressure ≤150/90 mm Hg

Study Design

- Anticipated enrollment: ~236 subjects



If remission is achieved, subjects are randomized to Acthar vs placebo for maintenance
Remission Achieved
Acthar 80 U SC 2x/week
Placebo 2x/week
Follow-up
Screening
Acthar 80 U SC 3x/week
Taper
No Remission
Acthar 80 U SC 3x/week
Taper
Follow-up
If remission is not achieved, subjects have the option of entering an OLE period
Screening (Days -63 to -3)
Open-label Treatment (Weeks 0-23)
Taper (Weeks 24-25)
Randomized Maintenance Treatment or OLE (Weeks 26-49)
Follow-up Period (Weeks 50-54/56)

Study Endpoints

Primary Endpoint

- Proportion of subjects who achieve CR or PR of proteinuria at Week 24

Key Secondary Endpoints

- Time to first relapse in subjects with CR or PR at Week 24 during the Randomized Maintenance Period
- Proportion of subjects
 - Who maintain remission of proteinuria at Week 50
 - With remission at Week 24 who experience relapse during the Randomized Maintenance Period
- Change in eGFR, total cholesterol, and uPCR from Week 24 to Week 50 in subjects with remission at Week 24

References

1. Malaga-Diequez L, Bouhassira D, Gipson D, Trachtman H. Novel therapies for FSGS: preclinical and clinical studies. *Adv Chronic Kidney Dis.* 2015;22(2):e1-6.
2. Korbet SM. Clinical picture and outcome of primary focal segmental glomerulosclerosis. *Nephrol Dial Transplant.* 1999;14(suppl 3):68-73.
3. Bose B, Cattran D, Toronto Glomerulonephritis Registry. Glomerular diseases: FSGS. *Clin J Am Soc Nephrol*. 2014;9(3):626-632.
4. Cattran DC, Alexopoulos E, Heering P, et al. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. *Kidney Int.* 2007;72(12):1429-1447.
5. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry Group. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. *J Am Soc Nephrol.* 2005;16(4):1061-1068.
6. Hogan J, Bomback AS, Mehta K, et al. Treatment of idiopathic FSGS with adrenocorticotropic hormone gel. *Clin J Am Soc Nephrol*. 2013;8(12):2072-2081.

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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CNI, calcineurin inhibitors; CR, complete remission; eGFR, estimated glomerular filtration rate; OLE, open-label extension; PR, partial remission; SC, subcutaneous; uPCR, urine protein-to-creatinine ratio.

RT01

A Prospective Observational Registry of H.P. Acthar® Gel for the Treatment of Multiple Sclerosis Relapse

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Introduction

- During the last several years, there has been tremendous expansion in the range of agents available to treat multiple sclerosis (MS)[1,2]
 - Several disease-modifying therapies (DMTs) are currently available, and several more are under investigation
 - DMTs reduce the occurrence of MS relapses, slow disability worsening, and decrease activity on magnetic resonance imaging
- Despite these advances in treatment, many patients with MS experience relapses
- High-dose corticosteroid therapy (eg, with methylprednisolone) is the mainstay of acute treatment of MS relapses[3,4]
 - Results from randomized, double-blind clinical trials suggest that 19% to 35% of patients may not adequately respond to this therapy[5,6]
- For patients who do not respond to or are unable to tolerate high-dose corticosteroids, options for acute treatment of relapses are limited
- Incomplete recovery from MS relapses may contribute to accrual of disability, highlighting the importance of effective relapse treatment[4,7,8]
- Repository corticotropin injection (RCI; H.P. Acthar Gel) contains a porcine-derived analogue of adrenocorticotropic hormone (ACTH) approved by the US Food and Drug Administration for treatment of MS relapses in adults[9]
 - Anti-inflammatory and immunomodulatory effects of ACTH in MS historically were attributed solely to its ability to stimulate endogenous cortisol, but more recent evidence suggests that corticosteroid-independent melanocortin receptor–mediated activity may contribute[10]
- Study objectives
 - Characterize the population of patients who receive RCI for MS relapses
 - Identify treatment patterns, MS relapse recovery, and safety outcomes
- This interim report summarizes data collected through October 27, 2016

Methods

Study Design

- Ongoing multicenter, prospective, 24-month, observational registry study
- Target enrollment: 260 patients at up to 60 sites (ie, neurology practices in the United States that treat adult patients with MS)

Enrollment and Data Collection

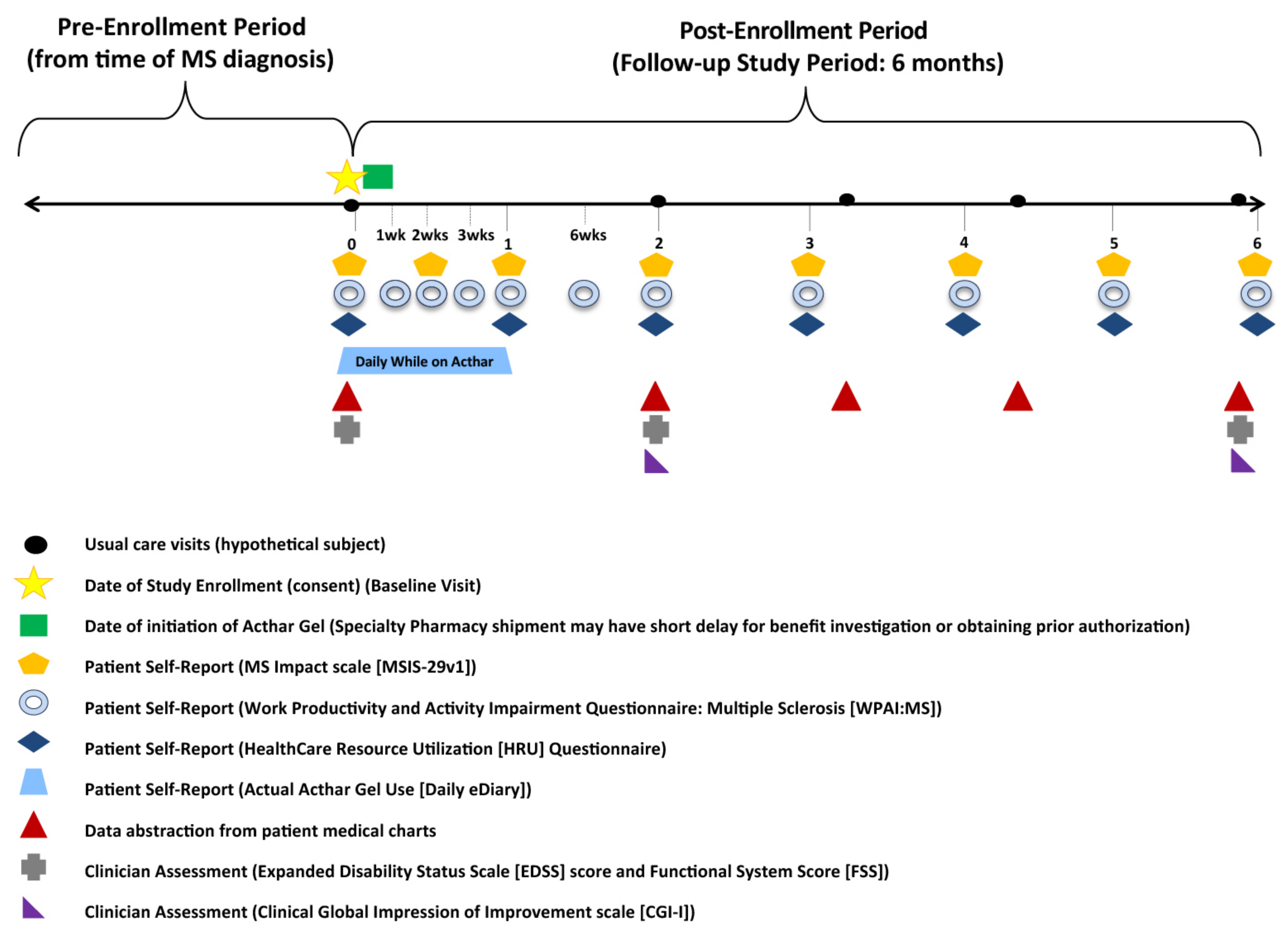
- Potentially eligible patients are recruited during routine care visits at the study sites
 - Those who meet the study eligibility criteria (**Table 1**) and provide informed consent are enrolled

Table 1: Key Inclusion and Exclusion Criteria

Inclusion
Age ≥18 years
Clinically definite relapsing form of MS according to McDonald criteria (2010 revision)[11]
Acute MS exacerbation as determined by treating clinician
Planning to initiate RCI therapy for acute MS exacerbation
Exclusion
Diagnosis of progressive MS
Requirement for concomitant corticosteroid therapy
Receiving experimental drug therapy
History (within 5 years) of scleroderma, systemic fungal infections, ocular herpes simplex, or cancer
Recent surgery or a history (within 6 months) or presence of a peptic ulcer, congestive heart failure, or sensitivity to proteins of porcine origin
Pregnancy, breastfeeding, or (if woman of childbearing potential) unwillingness to use appropriate contraception
Abbreviations: MS, multiple sclerosis; RCI, repository corticotropin injection.

- Each patient will be followed up for a minimum of 6 months and a maximum of 24 months
- Data will be abstracted from patient medical records at predefined time points (**Figure 1**)
- RCI will be obtained via the usual commercial channels for prescription medications
- While receiving RCI, patients will record data on daily RCI use in electronic diaries (**Figure 1**)
- Patients will also complete the following self-report instruments at the times specified in **Figure 1**
 - 29-item Multiple Sclerosis Impact Scale, version 1 (MSIS-29v1)
 - 6-question Work Productivity and Activity Impairment questionnaire for multiple sclerosis (WPAI:MS)
 - 5-question healthcare resource utilization (HRU) questionnaire
- The clinician assessments below will be administered at the times depicted in **Figure 1**
 - Expanded Disability Status Scale (EDSS) and Functional System Score (FSS)
 - Clinical Global Impression of Improvement (CGI-I) scale

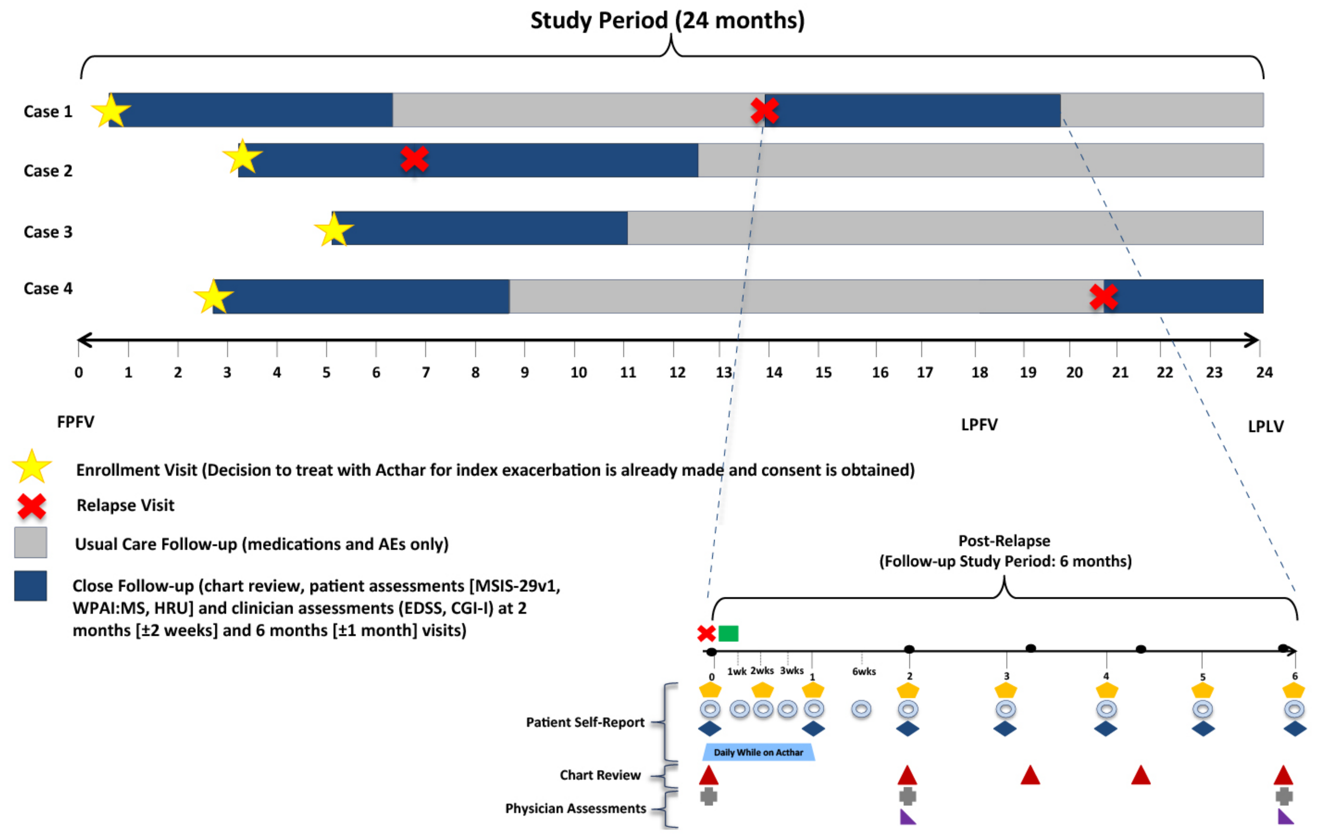
Figure 1. Patient Enrollment and Data Collection Overview[a,b]


Pre-Enrollment Period
(from time of MS diagnosis)
Post-Enrollment Period
(Follow-up Study Period: 6 months)
0
1wk
2wks
3wks
1
6wks
2
3
4
5
6
Daily While on Acthar
Usual care visits (hypothetical subject)
Date of Study Enrollment (consent) (Baseline Visit)
Date of initiation of Acthar Gel (Specialty Pharmacy shipment may have short delay for benefit investigation or obtaining prior authorization)
Patient Self-Report (MS Impact scale [MSIS-29v1])
Patient Self-Report (Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis [WPAI:MS])
Patient Self-Report (HealthCare Resource Utilization [HRU] Questionnaire)
Patient Self-Report (Actual Acthar Gel Use [Daily eDiary])
Data abstraction from patient medical charts
Clinician Assessment (Expanded Disability Status Scale [EDSS] score and Functional System Score [FSS])
Clinician Assessment (Clinical Global Impression of Improvement scale [CGI-I])

[a] Patients who experience post-enrollment relapses while the study is ongoing will be followed up for the relapse as specified for the index exacerbation (ie, for 6 months) or until study close (if the latter occurs before 6 months have elapsed). *Index exacerbation* is defined as the MS exacerbation at study enrollment.
[b] SAEs will be reported within 24 hours of identification, even when outside of usual care visits.
Abbreviations: MS, multiple sclerosis; SAE, serious adverse event.

- Because patients may have >1 MS exacerbation during the follow-up period, the exacerbation at study enrollment is defined as the *index exacerbation*, and subsequent exacerbations are defined as *relapses*
 - Relapses that occur during the study will be followed up as specified for the index exacerbation (ie, for 6 months) or until the study ends (if the latter occurs before 6 months have elapsed) (**Figures 1 and 2**)

Figure 2. Data Collection Schematic With Case Examples


Study Period (24 months)
Case 1
Case 2
Case 3
Case 4
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
FPFV
LPFV
LPLV
Enrollment Visit (Decision to treat with Acthar for index exacerbation is already made and consent is obtained)
Relapse Visit
Usual Care Follow-up (medications and AEs only)
Close Follow-up (chart review, patient assessments [MSIS-29v1, WPAI:MS, HRU] and clinician assessments (EDSS, CGI-I) at 2 months [±2 weeks] and 6 months [±1 month] visits)
Post-Relapse
(Follow-up Study Period: 6 months)
Patient Self-Report
Chart Review
Physician Assessments
Daily While on Acthar

Abbreviations: AE, adverse event; CGI-I, Clinical Global Impression of Improvement; EDSS, Expanded Disability Status Scale; FPFV, first patient first visit; HRU, healthcare resource utilization; LPFV, last patient first visit; LPLV, last patient last visit; MSIS-29v1, 29-item Multiple Sclerosis Impact Scale, version 1; WPAI:MS, Work Productivity and Activity Impairment questionnaire for multiple sclerosis.

Results

Patient Characteristics and Medication Use at Enrollment

- As of October 27, 2016, 45 patients had enrolled in the study and provided data
- Patient characteristics and medication use at enrollment are shown in **Tables 2** and **3**, respectively
- 23 patients (51%) had a history of insufficient treatment response to, intolerance of, or intravenous access problems with high-dose corticosteroid therapy

Table 2. Patient Characteristics at Enrollment

Characteristic	Initial Screening (N=45)
Age,[a] mean (SD), y	50.2 (10.7)
Gender, No. (%)	
Male	5 (11)
Female	31 (69)
Missing	9 (20)
Race, No. (%)	
Black/African American	4 (9)
White	29 (64)
Hispanic	1 (2)
No information/missing	11 (24)
EDSS score,[b,c] mean (SD)	4.4 (1.9)
Previous treatments for MS, No. (%)	
Methylprednisolone	13 (29)
RCI	11 (24)
IV steroids (unspecified)	2 (4)
Prednisone	2 (4)
Glatiramer acetate	1 (2)
Teriflunomide	1 (2)
None	1 (2)
Unknown	1 (2)
No information	12 (27)
MSIS-29v1 physical section score,[d,e] mean (SD)	65.4 (19.4)

[a] Data were available for 36 patients. [b] Data were available for 27 patients. [c] Rated on a scale from 0 (normal neurologic exam) to 10 (death due to MS). [d] Data were available for 35 patients. [e] Scored on a scale from 0 to 100, with 100 representing the worst possible score.
Abbreviations: EDSS, Expanded Disability Status Scale; IV, intravenous; MSIS-29v1, 29-item Multiple Sclerosis Impact Scale, version 1; RCI, repository corticotropin injection; SD, standard deviation.

Table 3. Summary of Medication Use at Enrollment (N=45)

Characteristic	No. (%)
DMT use	
Yes	32 (71)
No	5 (11)
Missing	8 (18)
Specific DMT use[a]	
Dimethyl fumarate	15 (33)
Glatiramer acetate	9 (20)
Natalizumab	8 (18)
Alemtuzumab	5 (11)
Teriflunomide	5 (11)
Fingolimod	4 (9)
Interferon β-1a	2 (4)
Other concomitant medication/supplement use[a,b]	
Cholecalciferol	10 (22)
Ergocalciferol	8 (18)
Baclofen	7 (16)
Fampridine	6 (13)
Gabapentin	6 (13)
Cyanocobalamin	5 (11)
Multivitamins	5 (11)
Amantadine	3 (7)
Levothyroxine sodium	3 (7)
Topiramate	3 (7)

[a] Some patients were receiving >1 medication at time of enrollment. [b] Only medications used by ≥5% of patients are listed.
Abbreviations: DMT, disease-modifying therapy; RCI, repository corticotropin injection.

RCI Use

- Data on RCI use have been collected for 31 patients and are summarized in **Table 4**

Table 4. Summary of RCI Use (n=31)

	Median (IQR)
No. of doses per patient	5.0 (5.0)
Strength per dose, U	80 (0)
No. of days dosed[a]	5.0 (5.0)
Total dose per day, U	80 (0)

[a] RCI dosing was on 5 consecutive days for 22 patients (71%).
Note: RCI was injected subcutaneously in all patients who specified the mode of administration.
Abbreviations: IQR, interquartile range; RCI, repository corticotropin injection.

Safety

- 9 adverse events (AEs), including 3 serious adverse events (SAEs), have been reported (**Table 5**)
- All SAEs were considered not related or unlikely related to RCI, and all patients recovered

Table 5. Summary of AEs

Subject	AE Term	Considered Serious
A	Nausea	No
	Vomiting	No
	Headache	No
B	UTI	Yes
C	Trigeminal neuralgia	No
D	UTI	No
	Acute sinusitis	No
E	Asthenia	Yes
F	MS relapse	Yes

Abbreviations: AE, adverse event; MS, multiple sclerosis; SAE, serious adverse event; UTI, urinary tract infection.

Conclusions

- Data from this ongoing study will expand current understanding of RCI use for the treatment of MS relapses and will provide information regarding
 - Characteristics of patients treated with RCI
 - MS relapse treatment patterns
 - Treatment response and MS relapse recovery
 - RCI safety
 - Characteristics of patients who experience additional MS relapses (ie, following the index exacerbation) during the study period
- The data collected to date suggest that RCI is typically dosed using a regimen of 80 U/d for a period of 5 days
 - Additional data on RCI dosing and therapeutic response collected during the remainder of the study could be used to explore possible clinical implications for the treatment of MS relapses
- Study enrollment is anticipated to conclude by the end of 2017

References

1. Comi G, Radaelli M, Soelberg Sørensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet.* 2017;389(10076):1347-1356.
2. Doshi A, Chataway J. Multiple sclerosis, a treatable disease. *Clin Med (Lond).* 2016;16(suppl 6):s53-s59.
3. Berkovich R. Treatment of acute relapses in multiple sclerosis. *Neurotherapeutics.* 2013;10(1):97-105.
4. Kalincik T. Multiple sclerosis relapses: epidemiology, outcomes and management. A systematic review. *Neuroepidemiology.* 2015;44(4):199-214.
5. Le Page E, Veillard D, Laplaud DA, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. *Lancet.* 2015;386(9997):974-981.
6. Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J. Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology.* 1998;51(2):529-534.
7. Goodin DS, Reder AT, Bermel RA, et al. Relapses in multiple sclerosis: relationship to disability. *Mult Scler Relat Disord.* 2016;6:10-20.
8. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology.* 2003;61(11):1528-1532.
9. H.P. Acthar Gel [package insert]. Hazelwood, MO: Mallinckrodt Pharmaceuticals; 2015.
10. Arnason BG, Berkovich R, Catania A, Lisak RP, Zaidi M. Mechanisms of action of adrenocorticotropic hormone and other melanocortins relevant to the clinical management of patients with multiple sclerosis. *Mult Scler.* 2013;19(2):130-136.
11. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292-302.

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A Multicenter, Randomized, Double-blind, Placebo-Controlled Parallel-Group, Pilot Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS)

Mallinckrodt Pharmaceuticals

Background

- MS is a chronic neurodegenerative disease characterized by demyelination within the CNS
- According to the Multiple Sclerosis Foundation, between 300,000 and 400,000 people in the United States and ~2.5 million worldwide are estimated to have MS; MS is more common in women than men (3:1 ratio) and is most commonly diagnosed between 20 and 40 years of age, although it can develop in young children, teenagers, and older adults[1]
- The most common form of MS is RRMS, in which patients experience episodes of worsening neurological function followed by periods of partial or complete recovery
- MS relapses are treated with high-dose corticosteroids or ACTH for patients who do not respond to or tolerate corticosteroids
- In randomized trials, 20%-35% of patients treated with corticosteroids do not have significant improvements in MS relapses or related symptoms[2,3]
- Acthar is approved for treating MS exacerbations and is an option for patients who do not respond to standard of care treatment with high-dose corticosteroids[4-6]

Purpose

- The purpose of this study is to determine the efficacy and safety of Acthar in subjects with RRMS who have not responded adequately to treatment with high-dose corticosteroids

Objectives

- The primary objectives of this study are to generate an estimate of the response rate for Acthar and assess its safety and tolerability in subjects with RRMS who have not responded to high-dose IVMP, oral prednisone, or oral methylprednisolone

Patients with progressing MS experience a steady worsening of symptoms that frequently affects mobility, but the rate of progression varies widely according to the extent of nerve damage and the nerves affected.[1]

Image Source: Wavebreakmedia/Shutterstock.com. Accessed September 11, 2017.

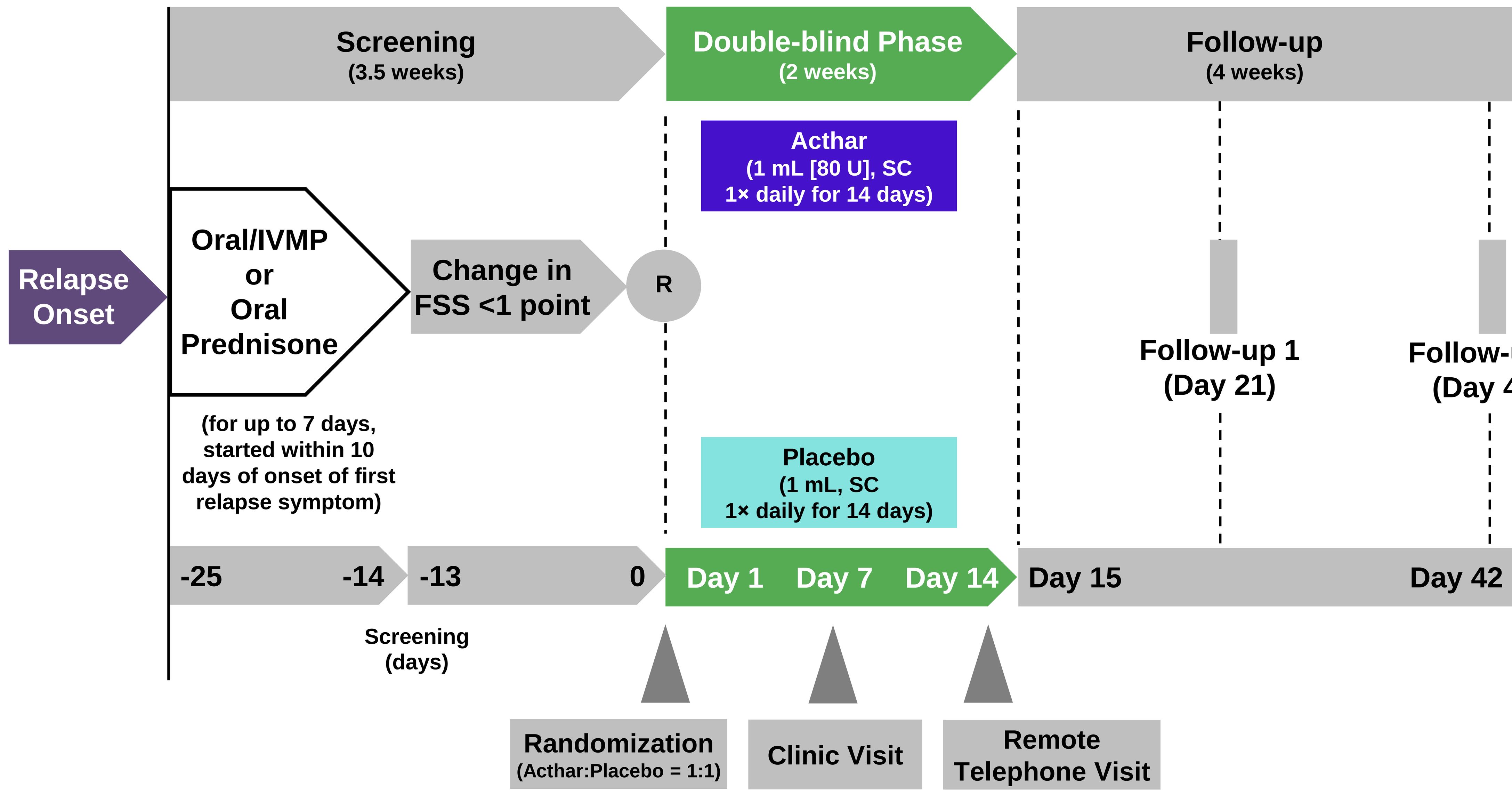


Study Population

- Adult males or females with RRMS
- Onset of relapse ≤25 days before the Baseline visit
- Treatment with corticosteroids within 10 days of relapse symptom onset
 - IVMP (1 g/day) OR
 - Oral prednisone (1250 mg/day) OR
 - Oral methylprednisolone (1000 mg/day)
- Failure to improve by at least 1 point in 1 or more FSS functions 14 days after the first dose of corticosteroids
- An EDSS score of 3.5 to 6.5 at the Baseline visit

Study Design

- Anticipated enrollment: ~66 subjects



Screening (3.5 weeks)
Double-blind Phase (2 weeks)
Follow-up (4 weeks)
Acthar (1 mL [80 U], SC 1× daily for 14 days)
Relapse Onset
Oral/IVMP or Oral Prednisone
Change in FSS <1 point
R
Follow-up 1 (Day 21)
Follow-up 2 (Day 42)
(for up to 7 days, started within 10 days of onset of first relapse symptom)
Placebo (1 mL, SC 1× daily for 14 days)
-25 -14 -13 0 Day 1 Day 7 Day 14 Day 15 Day 42
Screening (days)
Randomization (Acthar:Placebo = 1:1)
Clinic Visit
Remote Telephone Visit

Study Endpoints

Primary Endpoints

Efficacy

- Response rate based on the EDSS on Day 42 for each treatment group

Safety

- Summary of safety profile, including AEs (serious and nonserious), vital signs, and laboratory assessments, by study period and over the entire study

Secondary Endpoints

- For each treatment group
 - Response rates based on the MSIS-29 on Days 7, 14, 21, and 42
 - Response rates based on the EDSS on Days 7 and 21
 - CGI-I mean scores on Days 7, 21, and 42

References

1. Multiple Sclerosis Foundation. Common Questions. https://msfocus.org/Facts-About-MS.aspx. Accessed September 5, 2017.
2. Le Page E, Veillard D, Laplaud DA, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. *Lancet*. 2015;386(9997):974-981.
3. Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J. Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology*. 1998;51(2):529-534.
4. Rose AS, Kuzma JW, Kurtzke JF, et al. Cooperative study in the evaluation of therapy in multiple sclerosis. ACTH vs. placebo - final report. *Neurology*. 1970;20(5):1-59.
5. Miller H, Newell DJ, Ridley A. Multiple sclerosis. Treatment of acute exacerbations with corticotrophin (ACTH). *Lancet*. 1961;2:1120-1122.
6. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS. *Neurology*. 1989;39(7):969-971.

INVESTOR DAY ◆ OCTOBER 4, 2017 ◆ NEW YORK, NY

Abbreviations: ACTH, adrenocorticotrophic hormone; AE, adverse event; CI, confidence interval; CNS, central nervous system; EDSS, Expanded Disability Status Scale; FSS, Functional Systems Score; IVMP, intravenous methylprednisolone; MS, multiple sclerosis; MSIS-29, Multiple Sclerosis Impact Scale; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous.

Treatment with repository corticotropin injection reduces the progression of experimental autoimmune uveitis in rats

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Mallinckrodt Pharmaceuticals

ABSTARCT

Purpose: Previous studies have suggested that melanocortin receptor (MCR) agonists play a role in regulating the progression and resolution of experimental autoimmune uveitis (EAU). Repository corticotropin injection (RCI: H.P. Acthar® Gel) is a complex formulation containing a porcine ACTH analogue. ACTH is a melanocortin peptide that binds to the 5 known MCRs. Because RCI is an FDA-approved treatment for certain inflammatory ocular disorders, the aim of this study was to investigate the effects of RCI on a preclinical model of EAU.

Method: Lewis rats were immunized with interphotoreceptor retinoid binding protein (IRBP) peptide (1177-1191) in complete Freud's adjuvant. Inflammation was observed under a dissection microscope on days 4, 7, 11 and 14 post immunization and disease was clinically scored (as described in Figure 1) on a scale of 0-4 based on their anterior clinical disease. Animals were subcutaneously dosed with RCI (10, 40, or 400 IU/kg), Placebo gel (5mL/kg) or Prednisolone (0.1, 1, or 5 mg/kg) every other day starting on the first day of the study. On day 14, whole eyes were collected, processed and sections were stained with hematoxylin & eosin and scored.

Results: Clinical assessment within the anterior chamber of the eye performed in a blinded manner, demonstrated that RCI administered at 40 or 400 IU/kg significantly reduced the ocular clinical disease score on day 14 compared to placebo (0.93 ± 0.18 and 0.85 ± 0.17 versus 1.98 ± 0.22, respectively), ($p \leq 0.01$). In contrast, prednisolone marginally reduced the clinical disease score, at the doses tested, with only the 1 mg/kg dose having significance (1.05 ± 0.18; $p \leq 0.05$). In addition, the clinical findings for RCI were supported by the histological data, showing protection to the retinal architecture with a reduction in inflammation at all 3 doses evaluated.

Conclusions: The treatment of EAU with RCI resulted in the suppression of the ocular clinical score and inflammation reducing retinal damage. These data are the first to explore the effects of RCI in a preclinical model of experimental autoimmune uveitis.

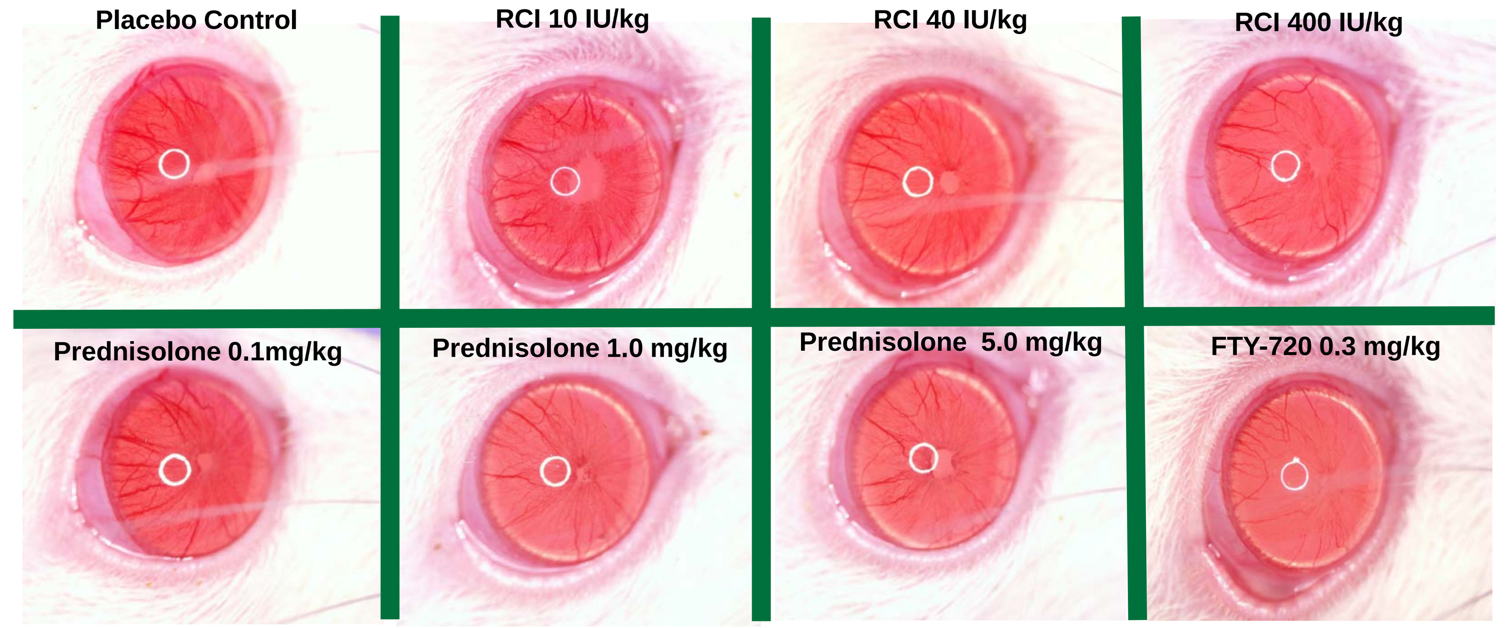
RESULTS

FIGURE 1: Clinical Evaluations: Animals were observed under a dissection microscope and scored on a scale of 0-4 based on their anterior clinical disease. Representative images of the anterior chamber were taken at the time of clinical evaluations (A). Treatment with RCI significantly reduced the ocular clinical score (mean ± SEM) on Days 11 (B) and 14 (C) for the mid and high doses. Treatment with prednisolone showed a trend in the clinical score reduction, with significance at the 5 mg/kg dose on day 11 and for the 1 mg/kg dose on day 14.

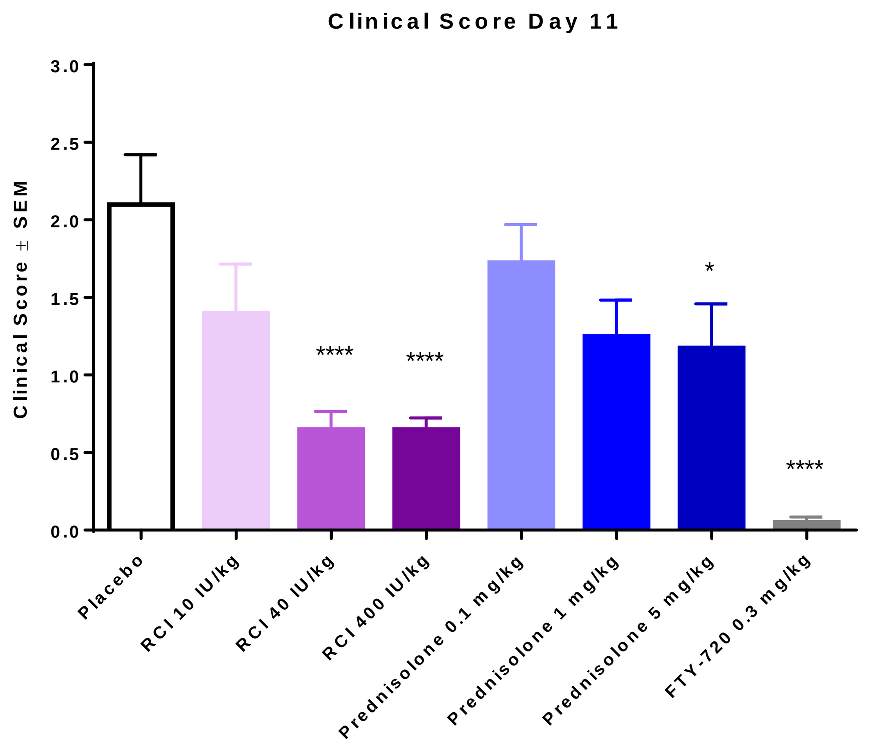
(*p < 0.05; ***p < 0.01; ***p < 0.001 ****p < 0.0001) one-way ANOVA Dunnett's test.

Clinical Scoring Scale
0-0.5: No disease; eye is translucent. Some blood vessels in the iris may be dilated.
1: Engorged blood vessels in iris; abnormal pupil contraction (or dilation).
2: Slight haziness to the anterior chamber.
3: Moderately opaque anterior chamber, but pupil still visible.
4: Opaque anterior chamber and obscured pupil

A


Placebo Control
RCI 10 IU/kg
RCI 40 IU/kg
RCI 400 IU/kg
Prednisolone 0.1mg/kg
Prednisolone 1.0 mg/kg
Prednisolone 5.0 mg/kg
FTY-720 0.3 mg/kg

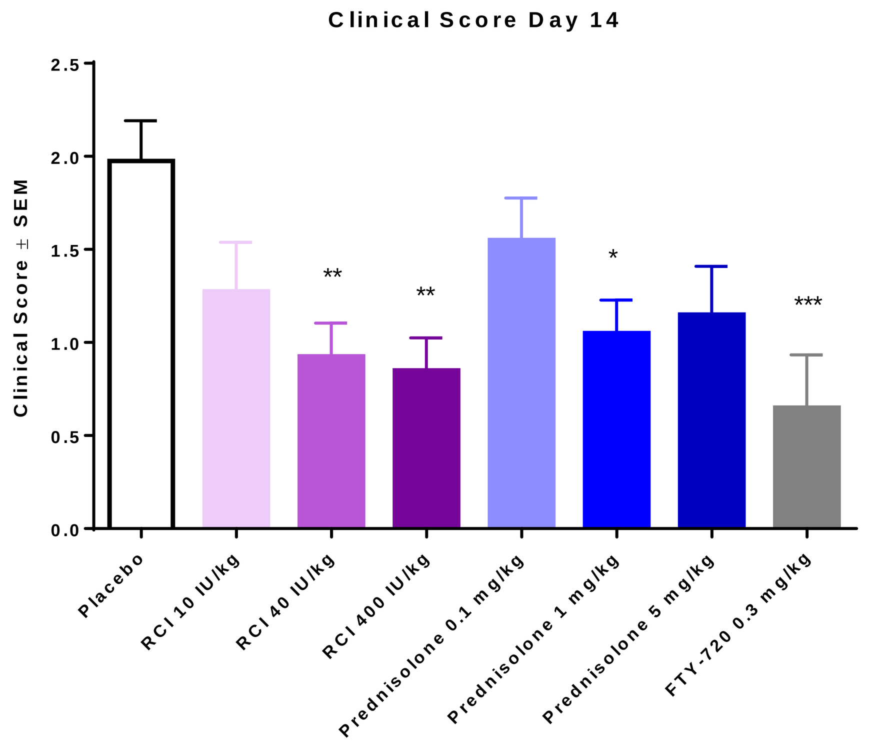
B


Clinical Score Day 11
Clinical Score ± SEM
3.0
2.5
2.0
1.5
1.0
0.5
0.0

*

Placebo
RCI 10 IU/kg
RCI 40 IU/kg
RCI 400 IU/kg
Prednisolone 0.1 mg/kg
Prednisolone 1 mg/kg
Prednisolone 5 mg/kg
FTY-720 0.3 mg/kg

C


Clinical Score Day 14
Clinical Score ± SEM
2.5
2.0
1.5
1.0
0.5
0.0
**
**
*

Placebo
RCI 10 IU/kg
RCI 40 IU/kg
RCI 400 IU/kg
Prednisolone 0.1 mg/kg
Prednisolone 1 mg/kg
Prednisolone 5 mg/kg
FTY-720 0.3 mg/kg

FIGURE 2: HISTOPATHOLOGY SCORE
Following the clinical evaluations on Day 14, animals were euthanized and eyes processed for histology. A blinded grader analyzed the slides and scored utilizing the scoring system below. All concentrations of RCI tested provided significant protection (p>0.01, one-way ANOVA Dunnett's test versus placebo control group) to the retina. The high dose prednisolone also significantly reduced the scores compared to the placebo group (p>0.05, one-way ANOVA Dunnett's test). Representative histopathology photos

Histology Scoring Scale
0: No disease, normal retinal architecture.
0.5: Trace. <1/4 Mild inflammatory cell infiltration of the retina with or without photoreceptor damage.
1: ≥1/4 Mild inflammation and/or photoreceptor outer segment damage
2: ≥1/4 Mild to moderate inflammation and/or lesion extending to the outer nuclear layer.
3: ≥1/4 Moderate to marked inflammation and/or lesion extending to the inner nuclear layer.
4: ≥1/4 Severe inflammation and/or full-thickness retinal damage.

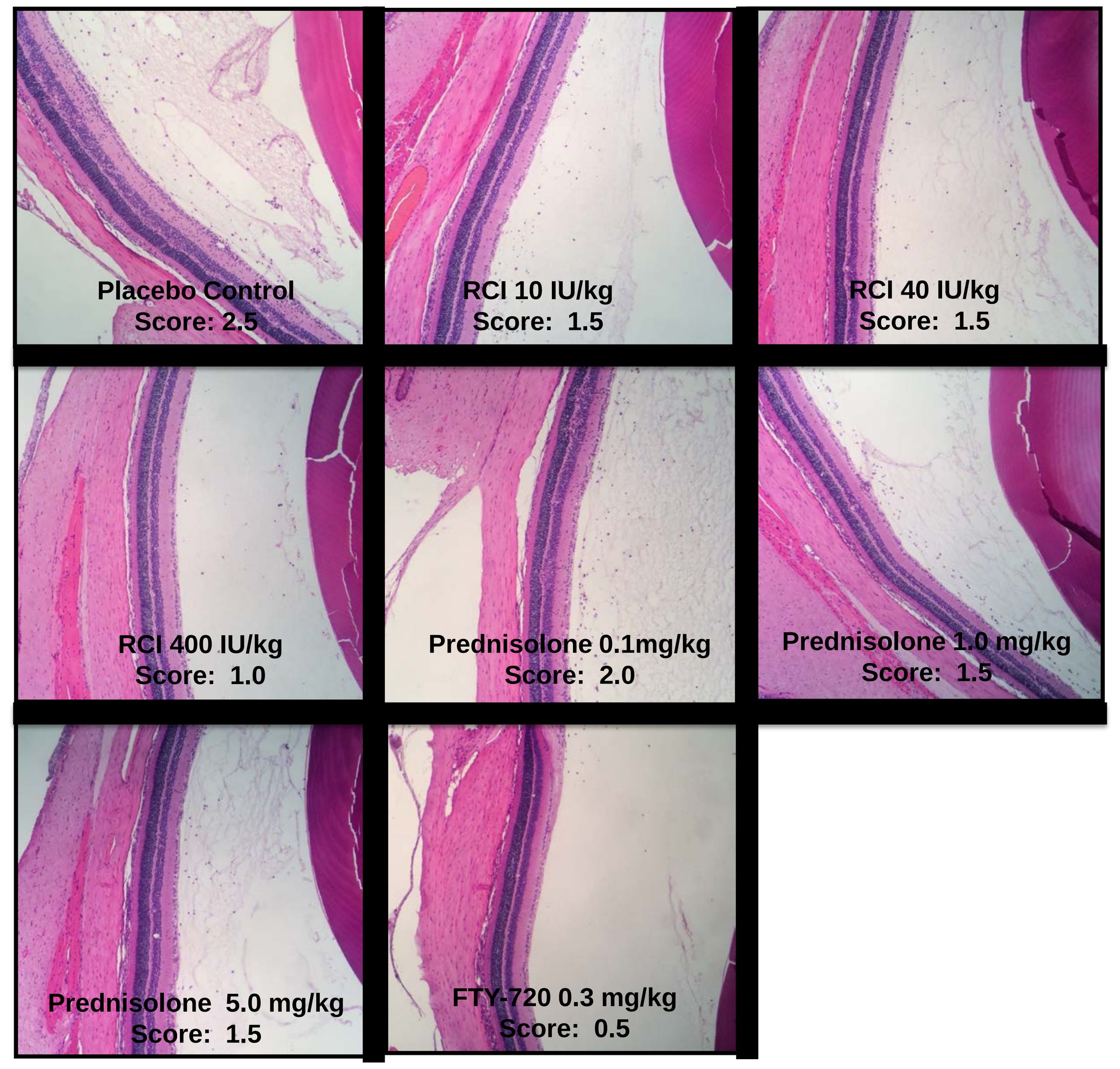

Placebo Control
Score: 2.5
RCI 10 IU/kg
Score: 1.5
RCI 40 IU/kg
Score: 1.5
RCI 400 IU/kg
Score: 1.0
Prednisolone 0.1mg/kg
Score: 2.0
Prednisolone 1.0 mg/kg
Score: 1.5
Prednisolone 5.0 mg/kg
Score: 1.5
FTY-720 0.3 mg/kg
Score: 0.5

Table 1. Melanocortin receptor expression in rat ocular tissue.
+, mRNA expression CT ≤ 31; (+) weak mRNA expression, 32 ≤ CT < 34; no mRNA expression, CT value ≥ 34.

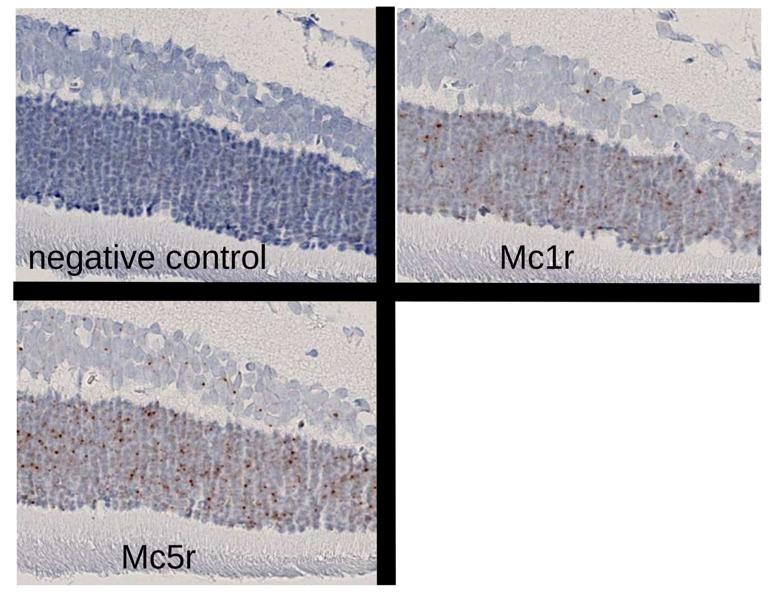
Mc1r	Mc2r	Mc3r	Mc4r	Mc5r
+	(+)	-	-	+

CT = cycle time

Table 2: Individual scoring of the histopathology evaluations. Significant values (p>0.05) are highlighted in green for reduced inflammatory damage compared to placebo control. Significant difference, as measured by the board certified pathologist, are highlighted in green (p ≤ 0.05, one-way ANOVA Dunnett's test)

Treatment Group 20 eyes/group	OD	OS
Placebo	2.43 ± 1.30	2.40 ± 1.15
RCI 10 IU/kg	**1.15 ± 0.71**	1.43 ± 1.01
RCI 40 IU/kg	**1.25 ± 0.75**	1.50 ± 0.84
RCI 400 IU/kg	**1.00 ± 0.53**	**1.05 ± 0.44**
Pred 0.1 mg/kg	1.70 ± 0.89	1.75 ± 0.68
Pred 1.0 mg/kg	1.70 ± 0.89	1.65 ± 1.08
Pred 5.0 mg/kg	**1.25 ± 0.82**	**1.20 ± 0.67**
FTY720 0.3 mg/kg	**0.75 ± 1.28**	**0.58 ± 0.79**

In situ hybridization was performed using the Advanced Cell Diagnostics RNAScope ISH platform. Custom designed ISH probe to rat Mc1r and Mc5r mRNA were use on formalin fixed, paraffin embedded sections. Images of retinal expression, focused within the outer nuclear layer with some minor expression in the inner layer.


negative control
Mc1r
Mc5r

SUMMARY

IRBP-induced uveitis was successfully induced in Lewis rats.
Disease control animals showed clinical signs of EAU, with increased redness, neovascularization, and haziness in the anterior chamber.

- Treatment with RCI at 40 and 400 IU/kg significantly alleviated clinical signs on Days 11 and 14.
- Prednisolone tested at three different concentrations showed a trend in reduced symptoms; however, only the high dose (5 mg/kg) on Day 11 and the mid dose (1 mg/kg) on Day 14 scored significantly less than placebo.

Histopathology scores supported the clinical findings.

- All three doses of RCI tested provided protection to the retinal architecture in addition to a reduction in the ocular inflammation.
- Prednisolone at 5 mg/kg) also significantly reduce the retinal damage and ocular inflammation versus the placebo.

Melanocortin receptors are uniquely expressed within the eye.

- Using quantitative-PCR, expression of Mc1r and Mc5r was seen in the eye. The level of mRNA for Mc2r showed weak expression.
- Utilizing *in situ* hybridization, Mc1r and Mc5r in the retina.

CONCULSION

We show RCI (H.P. Acthar® Gel) can reduces the progression of IRBP-induced uveitis. Additional studies will help elucidate RCI's mechanism(s) of action for immune suppression in uveitis. However, these data suggest RCI's potential anti-inflammatory effect in uveitis.

Studies were performed by Ophthalmic Research Associates Inc., Andover MA

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Suppression of acute uveitis following treatment with repository corticotropin injection

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Mallinckrodt Pharmaceuticals

INTRODUCTION

Repository corticotropin injection (RCI: H.P. Acthar® Gel) contains a purified porcine pituitary ACTH analogue, and is an FDA-approved treatment for several inflammatory eye diseases. ACTH binds to all 5 known melanocortin receptors and may suppress inflammation by steroid-dependent and independent pathways. Endotoxin-induced uveitis (EIU) in rodents is a useful experimental model to investigate mechanism of action and pharmacological efficacy of potential treatments. This study was conducted to investigate the potential anti-inflammatory benefit of RCI in an acute rat model of EIU. EIU is characterized by clinically relevant signs of inflammation, including elevated inflammatory cytokines and cellular inflammation in the anterior and vitreous chambers. Rats (16/group) were treated with dexamethasone (Dex), placebo, or RCI at 160 IU/kg, 400 IU/kg or 800 IU/kg following EIU induction. Eyes were clinically examined at pre-challenge, 6-8, 24, and 48 hours post challenge using the Combined Draize and McDonald – Shadduck Scoring System.

We show that RCI treatment significantly reduced ocular inflammation and inflammatory cytokines in an EIU model of acute uveitis. The mechanism of action of RCI may involve more than the induction of corticosteroids, and will be explored further in future studies.

MATERIAL & METHODS

Induction of Endotoxin-induced Uveitis. Female Sprague Dawley rats were administered a single subcutaneous injection on Day 0 and Day 1 of Dexamethasone (Dex) at 2 mg/kg (Group 3), Placebo gel (Group 4), or RCI gel at 160 IU/kg (Group 5), 400 IU/kg (Group 6) or 800 IU/kg (Group 7). The non-treated group was used as a control for disease induction (Group 2). EIU was induced by footpad injection with 100 µL of lipopolysaccharide (LPS) at 10 mg/mL. Clinical evaluation of animals was conducted using slit–lamp and scored according to the Combined Draize and McDonald-Shadduck Scoring System and the Ocular Posterior Segment Scoring Scale. Animals were euthanatized 24 and 48 hours (8/group/time) after disease induction, one eye/animal was collected, fixed and paraffin-embedded. Five sagittal sections for each eye were stained with hematoxylin and eosin and assessed by a board certified Pathologist for inflammatory cell infiltration, hemorrhage, necrosis, congestion, edema using a scale from 0 to 5 as follows: 0= normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, or 5 = severe. Scores were combined to give a total inflammatory score for each section.

Tissue cytokine expression. To evaluate cytokine expression, protein extracts were isolated from Rat Retina/Uveal Tract of the other eye. Tissue lysates were assayed for IL-1α, IL-6, MCP-1, MIP-2 and TNF-α using Millipore's Milliplex Rat Cytokine/Chemokine Magnetic Bead Panel (EMD Millipore; RECYTMAG-65K) on the Luminex 100 platform.

LPS-Induced TNF-α Production. RCI or vehicle was administered subcutaneously at a volume of 5 ml/kg. LPS (*Escherichia coli* serotype 0111:B4; Sigma-Aldrich) was administered 1.0 h after compound injection at a dose of 300 ug/rat in a volume of 0.5 ml. Blood was collected in serum separator tubes via cardiac puncture 90 min after LPS injection, a time point corresponding to maximal TNF-α production.

RESULTS

Table 1. Melanocortin receptor expression in rat ocular tissue. +, mRNA expression CT ≤ 31; (+) weak mRNA expression, 32 ≤ CT < 34; no mRNA expression, CT value ≥ 34.

Mc1r	Mc2r	Mc3r	Mc4r	Mc5r
+	(+)	-	-	+

CT = cycle time

Figure 1. In situ hybridization was performed using the Advanced Cell Diagnostics RNAScope ISH platform. Custom designed ISH probes to rat Mc1r and Mcr mRNA were used on formalin fixed, paraffin embedded sections. Images of retinal expression, focused within the outer nuclear layer with some minor expression in the inner layer.

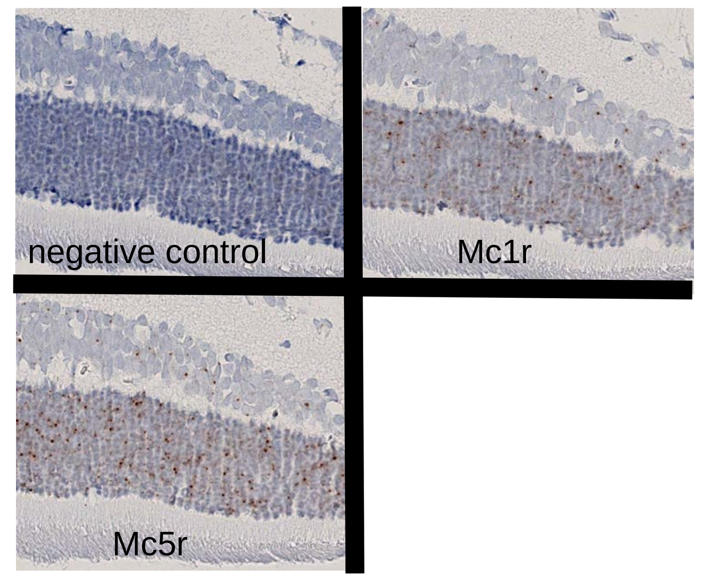
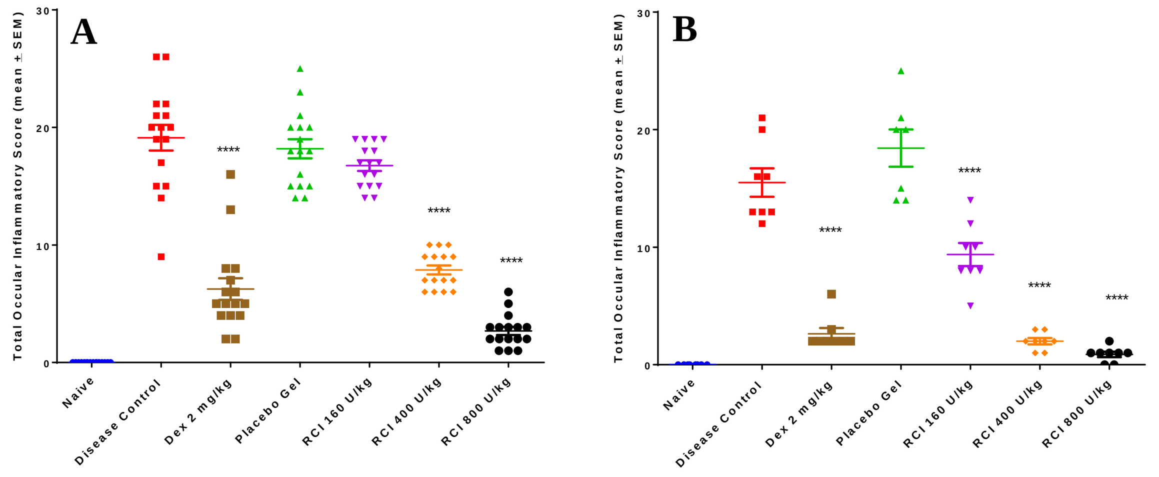
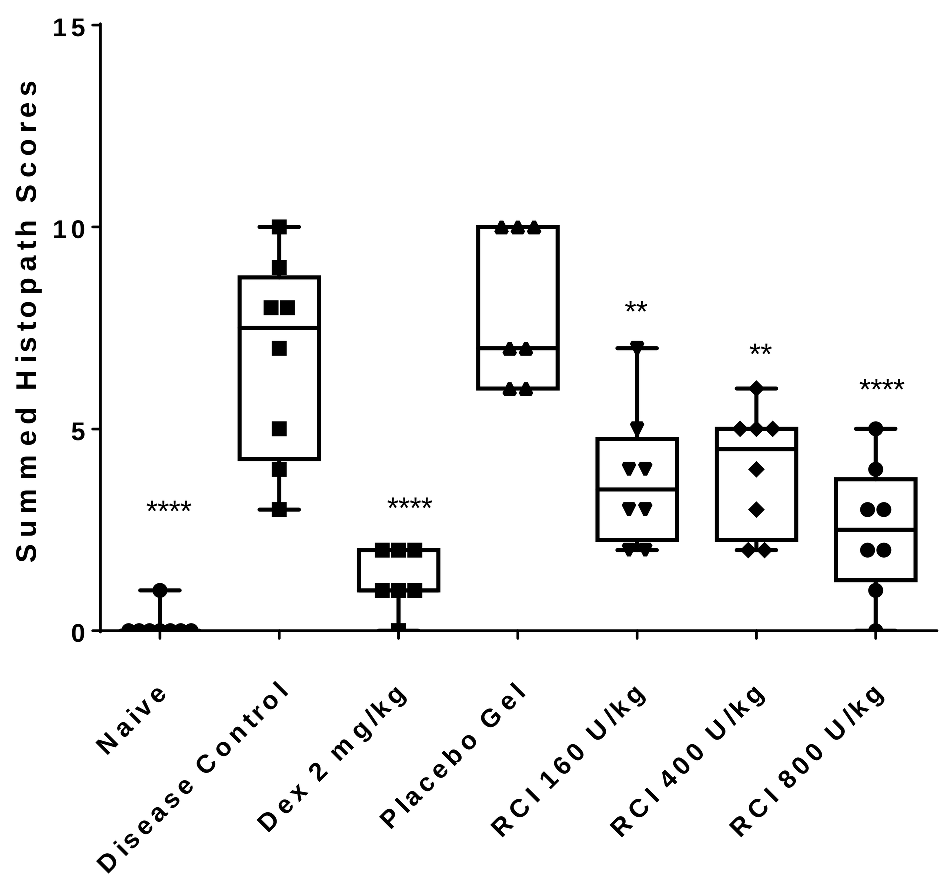

negative control
Mc1r
Mc5r

FIGURE 2. RCI treatment reduced the ocular inflammation score in the Endotoxin-induced Uveitis model, (A) 18 hour and (B)48 hour post-LPS injection. Symbols represent individual animal scores with mean +/- SEM. RCI at 160 U/kg significantly reduced ocular inflammation at 48 hours whereas 400 U/kg and 800 U/kg (****p < 0.0001, one-way ANOVA Dunnett's test) significantly inhibited ocular inflammation at all time points evaluated compared to Disease control animals.


A
B
Total Ocular Inflammatory Score (mean ± SEM)
30
20
10
0

Naive
Disease Control
Dex 2 mg/kg
Placebo Gel
RCI 160 U/kg
RCI 400 U/kg
RCI 800 U/kg

FIGURE 3: Treatment with RCI decreases the summed histopathology score 48 hour post LPS. Endotoxin-induced Uveitis leads to an acute inflammatory response composed largely of neutrophils and macrophages. This leads to an inflammatory response that is observed predominantly in the anterior chamber segment of the eye. (p ≤ 0.01, one-way ANOVA Dunnett's test versus disease control group)


Summed Histopath Scores
15
10
5
0

**
Naive
Disease Control
Dex 2 mg/kg
Placebo Gel
RCI 160 U/kg
RCI 400 U/kg
RCI 800 U/kg

FIGURE 4: HISTOPATHOLOGY IMAGES. Sagittal sections were stained with hematoxylin and eosin and assessed for inflammation and edema. Ocular inflammation at 48 hours showed an increase in neutrophils and macrophage in the anterior chamber, ciliary body and retina. Treatment with RCI dose-dependently reduced inflammation, edema, and the presence of proteinaceous fluid. A, Group 1; B, Group 2; C, Group 3; D, Group 4l; E, Group 5; F, Group 6; G, Group 7

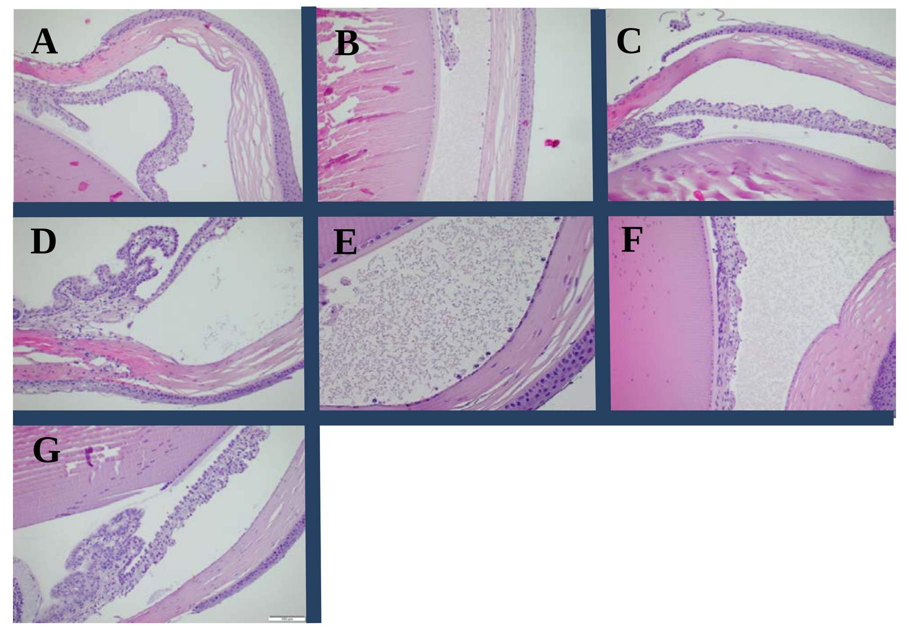
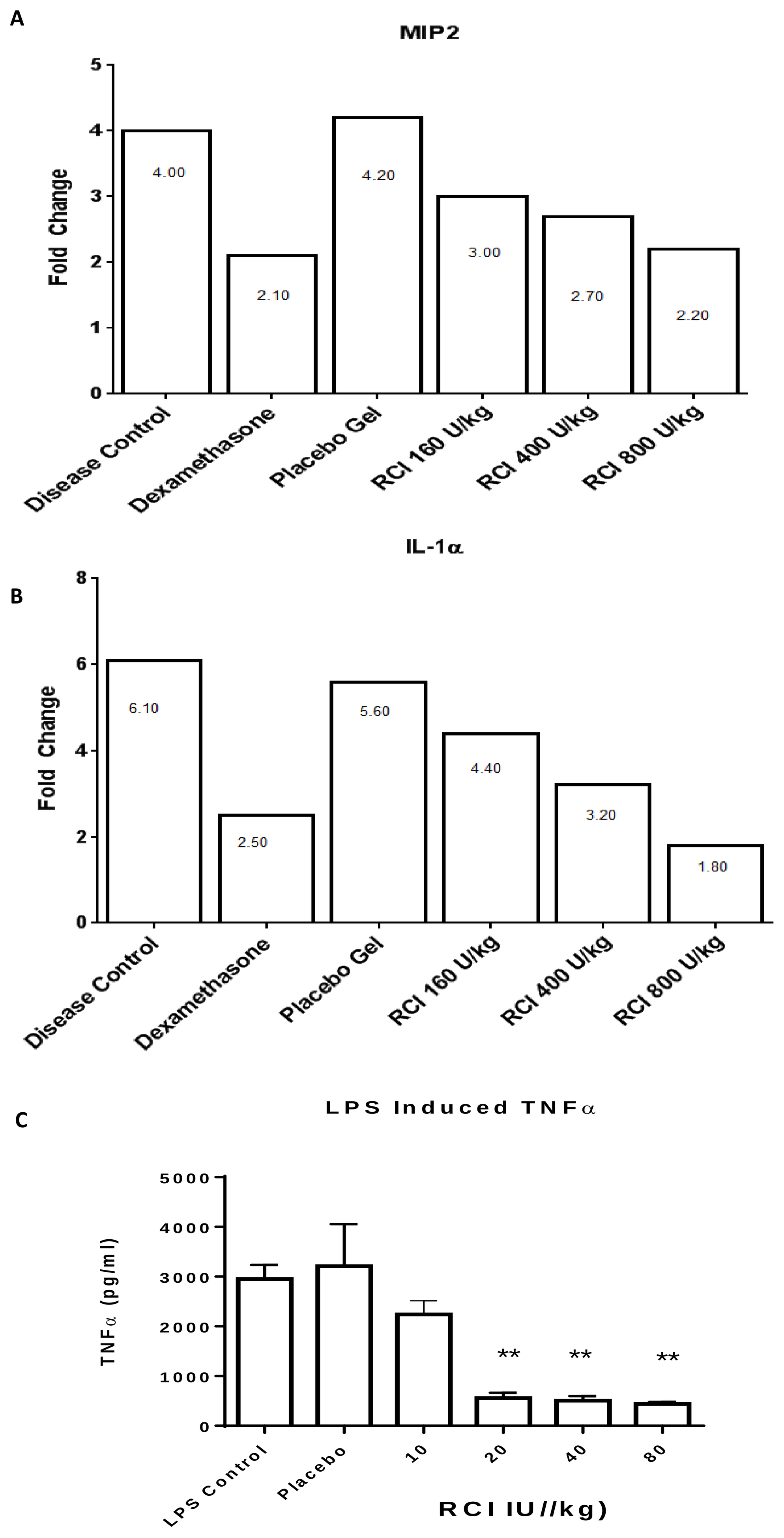

A
B
C
D
E
F
G

FIGURE 5: Reduction in inflammatory cytokines MIP-2, IL-1α, and TNFα following treatment with RCI. Eyes were collected at 18 hours. Tissue lysates were tested for IL-1α, IL-6, MCP1, MIP2, and TNFα. Only MIP2 (A) and IL-1α (B) showed a response to LPS challenge at 18 hours, and both were dose-dependently decreased by RCI. To examine the effects of RCI on TNFα (C) production, Sprague Dawley rats were treated with RCI (10, 20, 40, 80 U/kg) and challenged with LPS. RCI significantly reduced serum TNFα levels. (p ≤ 0.01, one-way ANOVA Dunnett's test versus disease control group)


A
MIP2
Fold Change
4.00
2.10
4.20
3.00
2.70
2.20
Disease Control
Dexamethasone
Placebo Gel
RCI 160 U/kg
RCI 400 U/kg
RCI 800 U/kg
B
IL-1α
6.10
2.50
5.60
4.40
3.20
1.80
C
LPS Induced TNFα
TNFα (pg/ml)
5000
4000
3000
2000
1000
0
**
LPS Control
Placebo
10
20
40
80
RCI IU//kg)

SUMMARY

Treatment Group	Ocular Clinical Score (mean ± sem)	IL-1α (pg/ml) (mean ± sem)	MIP2 (pg/ml) (mean ± sem)
Group 1 (Naïve)	0	37 ± 8.5*	62 ± 6.0*
Group 2 (Disease Control)	15.5 ± 1.2	207 ± 69	240 ± 47
Group 3 (Dex 2 mg/kg)	2.6 ± 0.5*	54 ± 11*	92 ± 10*
Group 4 (Placebo)	18.4 ± 1.6	135 ± 33	175 ± 28
Group 5 (RCI 160 IU/kg)	9.4 ± 1.0*	130 ± 35	158 ± 43
Group 6 (RCI 400 IU/kg)	2.0 ± 0.3*	96 ± 20	114 ± 18*
Group 7 (RCI 800 IU/kg)	0.9 ± 0.2*	51 ± 8.3*	126 ± 32*

* = p ≤ 0.05 in a one-way ANOVA Dunnett's test versus disease control group

Acute uveitis was successfully induced in Sprague Dawley rats. It was manifested in the anterior chamber of the eye, peaked at 18-24 hours and maintained out to 48 hours. Treatment with repository corticotropin injection significantly reduced ocular inflammation in a dose-dependent manner. RCI at 400 U/kg showed comparable level of reduction in clinical ocular symptoms to the positive control dexamethasone while treatment at 800 U/kg was shown to be even more efficacious. Pro-inflammatory chemokines and cytokines are thought to have a role in the recruitment of inflammatory cells and pathogenesis in uveitis. Cytokines such as IL-6 and TNF- α have been implicated the various clinical subtypes of uveitis, with aqueous humor levels correlating with disease severity (1,2). IL-1α and MIP2 were increased following LPS-induced uveitis. Treatment with RCI shows a dramatic and dose responsive reduction on the levels in the retina/uveal tract. Furthermore, in an LPS-induced TNF model, RCI significantly reduced TNFα production. The expression of Mc1r and Mc5r was show in the retina using quantitative PCR and *in situ* hybridization. In this study, RCI at 160, 400, and 800 U/kg showed dose-dependent suppression of the ocular inflammation and inflammatory cytokines induced in an experimental uveitis rat model. Additional studies are needed to elucidate RCI's mechanism(s) of action for immune suppression in uveitis. However, these data support the use of RCI in ophthalmic diseases.

REFERENCES

1. Rosenbaum JT, McDevitt RO, Guss RB, Egbert PR. (1980) Endotoxin-induce uveitis in rats as a model for human disease. Nature 286:611-613.
2. Ooi KG, Galatowicz G, Calder VL, Lightman SL. (2006) Cytokines and chemokines in uveitis: is there a correlation with clinical phenotype? Clin Med Res 4:294-309.

Acknowledgement: EIU was performed by Toxikon Corporation Bedford, MA

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A Multicenter, 2-Part Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in Subjects With Rheumatoid Arthritis (RA) With Persistently Active Disease

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Background

- RA is an autoimmune disorder characterized by chronic inflammation, articular erosions, and periarticular bone loss; prevalence is estimated at 0.5%-1% of the adult population in developed countries, with an annual incidence rate of 5-50 new cases per 100,000[1]
- The goal of treatment is focused on achieving remission (absence of inflammatory disease); low disease activity is an acceptable alternative
- Disease-modifying antirheumatic drugs (DMARDs) and corticosteroids are commonly used to manage RA, but 28%-58% of patients do not achieve a minimal 20% improvement in ACR criteria (ACR20)[2]; those patients who achieve improvement can experience a waning in response[3]
- Acthar is approved as an adjunctive therapy for short-term administration (to tide the patient over an exacerbation) in RA (selected cases may require low-dose maintenance therapy). An open-label single-center study suggested that 12 weeks of Acthar was an effective add-on therapy for patients with active RA refractory to at least 3 therapeutic agents with different mechanisms of action[4]

Purpose

- The purpose of this study is to confirm the efficacy of Acthar for the management of RA in patients who have persistent disease activity, with secondary evaluation of the potential benefit after LDA is achieved

Objectives

- The primary objective of this study is to assess the efficacy of Acthar given as a 1-mL (80 U) dose 2x/week for 12 weeks as determined by DAS28-ESR in subjects with persistently active RA
- Secondary objectives are to assess the safety and tolerability of Acthar as well as its efficacy to maintain LDA (in subjects who have achieved LDA after 12 weeks of treatment)

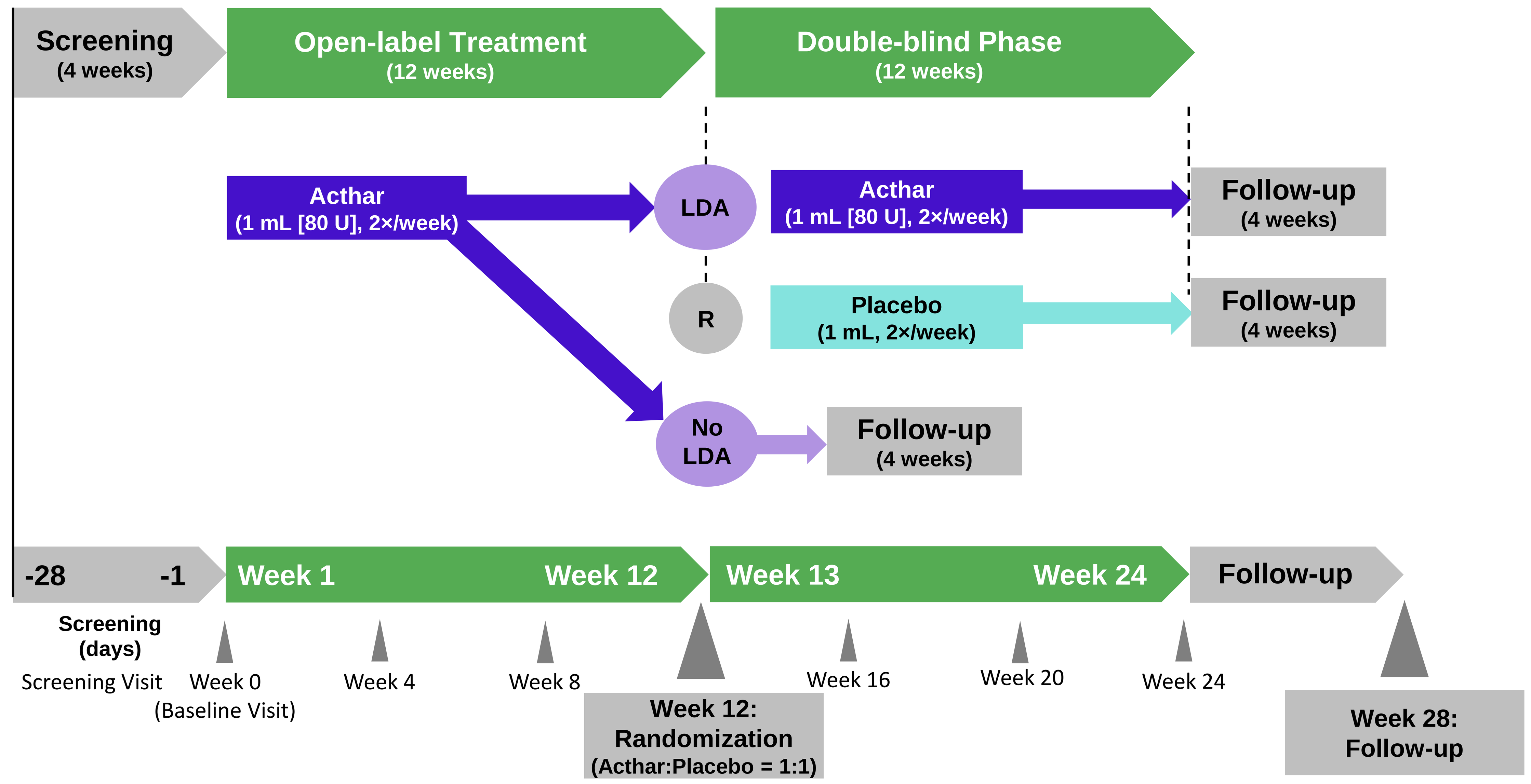
Study Population

- Diagnosis of RA screening
 - Per 2010 ACR/EULAR classification
- Persistently active disease
 - DAS28-ESR >3.2 (at screening and baseline)
- Corticosteroid, MTX, DMARD use for ≥12 weeks prior to screening*
 - Stable prednisone dose (5-10 mg) for ≥4 weeks prior to screening
 - MTX ≤20 mg per week + 1 allowed biologic or nonbiologic DMARD OR
 - 1 allowed biologic DMARD

*All starting dose levels must remain stable through the study duration.

Study Design

- Anticipated enrollment: ~232 subjects



Screening
(4 weeks)
Open-label Treatment
(12 weeks)
Double-blind Phase
(12 weeks)
Acthar
(1 mL [80 U], 2×/week)
LDA
Acthar
(1 mL [80 U], 2×/week)
Follow-up
(4 weeks)
R
Placebo
(1 mL, 2×/week)
Follow-up
(4 weeks)
No LDA
Follow-up
(4 weeks)
-28
-1
Week 1
Week 12
Week 13
Week 24
Follow-up
Screening
(days)
Screening Visit
Week 0
(Baseline Visit)
Week 4
Week 8
Week 12:
Randomization
(Acthar:Placebo = 1:1)
Week 16
Week 20
Week 24
Week 28:
Follow-up

Study Endpoints

Primary Endpoint

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

Secondary Endpoints

- Proportion of subjects
 - Who maintained DAS28-ESR <3.2 for Weeks 12-24
 - With CDAI ≤10 at Week 12
 - Who meet criteria for ACR20 at Week 12
- Time to disease activity flare for Weeks 12-24
- Summary of general safety profile (including the below) by study period and the entire study
 - AEs (serious and nonserious)
 - Vital signs
 - Laboratory assessments

References

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet.* 2010;376(9746):1094-1108.
2. Redlich K, Schett G, Steiner G, et al. Rheumatoid arthritis therapy after tumor necrosis factor and interleukin-1 blockade. *Arthritis Rheum.* 2003;48(12):3308-3319.
3. Finckh A, Simard JF, Gabay C, et al. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. *Ann Rheum Dis.* 2006;65(6):746-752.
4. Gillis T, Crane M, Hinkle C, Wei N. Repository corticotropin injection as adjunctive therapy in patients with rheumatoid arthritis who have failed previous therapies with at least three different modes of action. *Open Access Rheumatol.* 2017;9:131-138.

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Abbreviations: ACR, American College of Rheumatology; ACR20, 20% improvement in ACR criteria; ACTH, adrenocorticotropic hormone; AE, adverse event; CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score with 28 joint count and ESR; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; LDA, low disease activity; MTX, methotrexate; RA, rheumatoid arthritis.

A Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of H.P. Acthar® Gel in Subjects With Persistently Active Systemic Lupus Erythematosus (SLE) Despite Moderate-Dose Corticosteroids

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Background

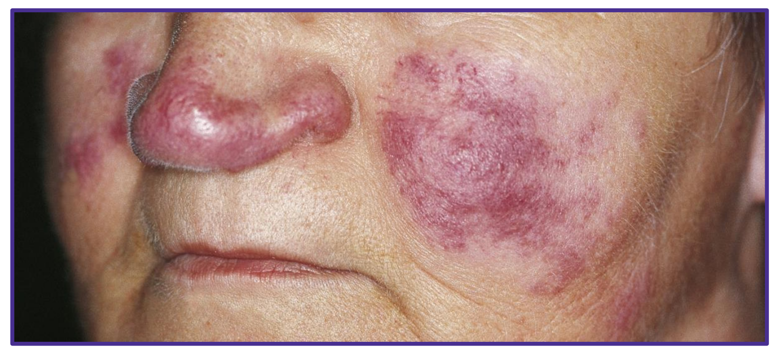
- SLE is a chronic, autoimmune disease that results in widespread inflammation and tissue damage to affected areas, including the joints, skin, brain, lungs, kidneys, and blood vessels;[1] ~1.5 million Americans and millions more worldwide have SLE[2]
- One-third of SLE-related deaths in the United States occur in patients younger than 45 years[3] despite declining mortality rates due to improvements in treatment and medical care
- A number of medications are used in the treatment of SLE, including NSAIDs, antimalarials, glucocorticoids, and immunosuppressive agents; the primary goal of treatment with these medications is to control or halt the inflammatory process while minimizing side effects
- Acthar is approved by the FDA for use during an exacerbation or as maintenance therapy in select cases of SLE
- Results from a recent randomized, double-blind, placebo-controlled pilot study as well as a single-center open-label investigation suggested that Acthar was an effective treatment alternative for reducing several measures of disease activity in patients with moderately active SLE[4,5]

Purpose

- The purpose of this study is provide additional data to support the efficacy and safety of Acthar in SLE and to further explore the PD, potential pharmacoeconomic, and steroid-sparing effects of Acthar

Objective

- The primary objective of this study is to determine the ability of Acthar to reduce SLE activity (as measured by SRI) in subjects requiring moderate-dose corticosteroids for persistently active disease



SLE can cause rashes or sores that appear on sun-exposed areas of skin.
Image Source:
Sand M, Sand D, Thrandorf C, Paech V, Altmeyer P, Bechara FG. https://commons.wikimedia.org/wiki/File:Lupus_pernio_01.jpg. Accessed September 1, 2017.

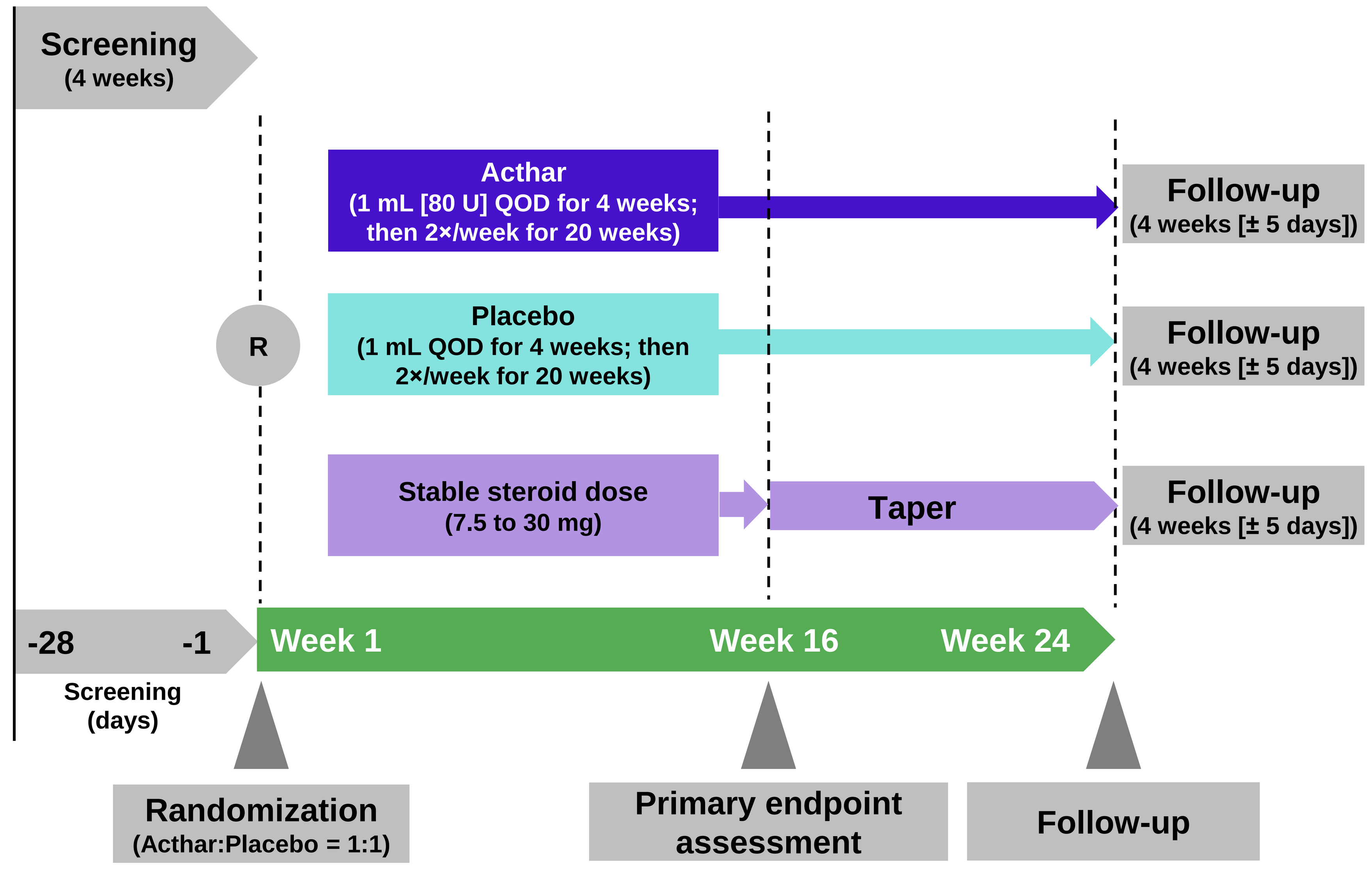
Study Population

- Diagnosis of SLE according to ACR revised criteria
- Active SLE as demonstrated by SLEDAI-2K score (arthritis and/or rash)*
- Moderate to severe arthritis and/or rash by BILAG-2004*
- Documented history or screening result of positive ANA, ENA, or anti-ds-DNA
- Corticosteroid use for ≥8 weeks prior to screening
 - Stable dose (7.5-30 mg) for ≥4 weeks prior to screening

* Must be present at Screening and Randomization Visits

Study Design

- Anticipated enrollment: ~162 subjects



Screening
(4 weeks)
R
Acthar
(1 mL [80 U] QOD for 4 weeks; then 2×/week for 20 weeks)
Placebo
(1 mL QOD for 4 weeks; then 2×/week for 20 weeks)
Stable steroid dose
(7.5 to 30 mg)
Taper
Follow-up
(4 weeks [± 5 days])
Follow-up
(4 weeks [± 5 days])
Follow-up
(4 weeks [± 5 days])
-28
-1
Screening
(days)
Week 1
Week 16
Week 24
Randomization
(Acthar:Placebo = 1:1)
Primary endpoint assessment
Follow-up

Study Endpoints

Primary Endpoint

- Proportion of responders as assessed by Systemic Lupus Erythematosus Responder Index (SRI) at Week 16

Secondary Endpoints

- Time to first response as assessed by SRI
- Change from baseline over time (Weeks 0 to 16) in the following disease activity measures
 - SLEDAI-2K
 - Total BILAG-2004
 - PGA
 - CLASI activity score (CLASI activity score at baseline)
 - 28-Joint Count (tender and swollen; tender and swollen joints at baseline)
- Proportion with decrease ≥4 points from baseline in SLEDAI-2K (Weeks 0 to 16)
- Summary of safety measures including
 - Vital signs
 - AEs (serious and non-serious)
 - Laboratory assessments

References

1. Centers for Disease Control and Prevention. Lupus Basic Fact Sheet. https://www.cdc.gov/lupus/basics/index.html. Accessed August 30, 2017.
2. Lupus Research Alliance. About Lupus. http://www.lupusny.org/about-lupus. Accessed August 30, 2017.
3. Centers for Disease Control and Prevention. Fact Sheet – Lupus. https://www.cdc.gov/media/pressrel/fs020503.htm. Accessed August 31, 2017.
4. Furie R, Mitrane M, Zhao E, Das M, Li D, Becker PM. Efficacy and tolerability of repository corticotropin injection in patients with persistently active SLE: results of a phase 4, randomised, controlled pilot study. *Lupus Sci Med.* 2016;3(1):e000180.
5. Fiechtner JJ, Montroy T. Treatment of moderately to severely active systemic lupus erythematosus with adrenocorticotropic hormone: a single-site, open-label trial. *Lupus*. 2014;23(9):905-912.

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Abbreviations: ACTH, adrenocorticotropic hormone; ANA, antinuclear antibody; BILAG-2004, British Isles Lupus Assessment Group:2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; ds, double strand; ENA, extractable nuclear antigens; FDA, Food and Drug Administration; hSLEDAI, Hybrid Systemic Lupus Erythematosus Disease Activity Index; IFA, immunofluorescent assay; NSAID, nonsteroidal anti-inflammatory drug; PD, pharmacodynamics; PGA, Physician's Global Assessment; QOD, every other day; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SRI, Systemic Lupus Erythematosus Responder Index.

Repository corticotropin injection exerts direct acute effects on human B cell gene expression distinct from the actions of glucocorticoids

Nancy J Olsen[1], Ann Benko[1],Carl McAloose[1], Teresa Sunyer[2], Patrice Becker[2], William J Kovacs[1]

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[2]Mallinckrodt ARD Inc., Hampton NJ USA

Introduction

Corticotropin (adrenocorticotropin, or ACTH) is the principal regulator of production of glucocorticoid hormones from the adrenal cortex. The discovery of anti-inflammatory properties of such glucocorticoids led directly to the use of ACTH preparations as therapeutic agents to augment endogenous glucocorticoid production; HP Acthar® Gel (repository corticotropin injection, RCI) is FDA approved for the treatment of certain inflammatory and autoimmune diseases. Both clinical observation (1,2) and experimental evidence (3) have, however, suggested that augmentation of endogenously produced glucocorticoid levels might not be the operative mechanism underlying all RCI effects. We used RNA-Seq methods to define the effects of RCI on human B lymphocytes at the molecular level and to compare the changes in gene expression resulting from RCI treatment with those resulting from glucocorticoid exposure.

Methods

Cell preparation and culture: Peripheral blood B cells from healthy volunteers were isolated with magnetic CD19 MicroBeads (Miltenyi Biotec). Cells were plated at 0.5-1.0 x 10^6/ml and stimulated with 10 ng/ml IL-4 and 2 µg/ml recombinant human CD40L (R&D Systems). Cells were also treated with either: (A) RCI (Mallinckrodt ARD, Inc.) at concentrations of 0.124 µM, 1.24 µM or 2.49 µM, (B) placebo gel identical to RCI but lacking active drug (Mallinckrodt ARD, Inc.), (C) dexamethasone (Dex) at 10 nM concentration, or (D) ethanol vehicle control for Dex. Cells were harvested at 19-24 hours.

RNA isolation, library preparation and sequencing: RNA was isolated from cells (RNeasy Mini Kit; QIAGEN), quantitated (Nanodrop 2000c spectrophotometer), and quality was determined (Agilent 2100 BioAnalyzer). A barcoded cDNA library from each sample was prepared using the TruSeq Stranded Total RNA with Ribo-Zero Gold Library Prep Kit (Illumina). Libraries were pooled, diluted, denatured, and loaded onto TruSeq SR v3 flow cells on an Illumina HiSeq 2500 for sequencing.

Quality control, mapping, quantification of RNA-Seq reads: Illumina CASAVA pipeline v1.8 was used to extract de-multiplexed sequencing reads and FastQC was used to validate raw sequence data. After alignment to the reference genome using TopHat (v 2.0.9) the read counts were calculated with HTSeq.

Differential gene expression analysis: RUVSeq R package v3.1 with edgeR was used to identify differentially expressed genes, comparing RCI with placebo gel and Dex with its own vehicle control.

Analysis of Interactions and Overrepresentation of Functional Pathways among RCI- and Dex-regulated mRNAs
STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) was used to analyze potential relationships among the mRNAs modulated by RCI or Dex (3). Interactions were quantitated using STRING by combining the probabilities from the different evidence channels and corrected for the probability of randomly observing an interaction. Evidence channels include experimental data from BIND, DIP, HPRD, IntAct, MINT, and PID and curated data from BioCyc, Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome. Overrepresentation of gene products in specific GO and KEGG pathways was assessed using STRING.

Results

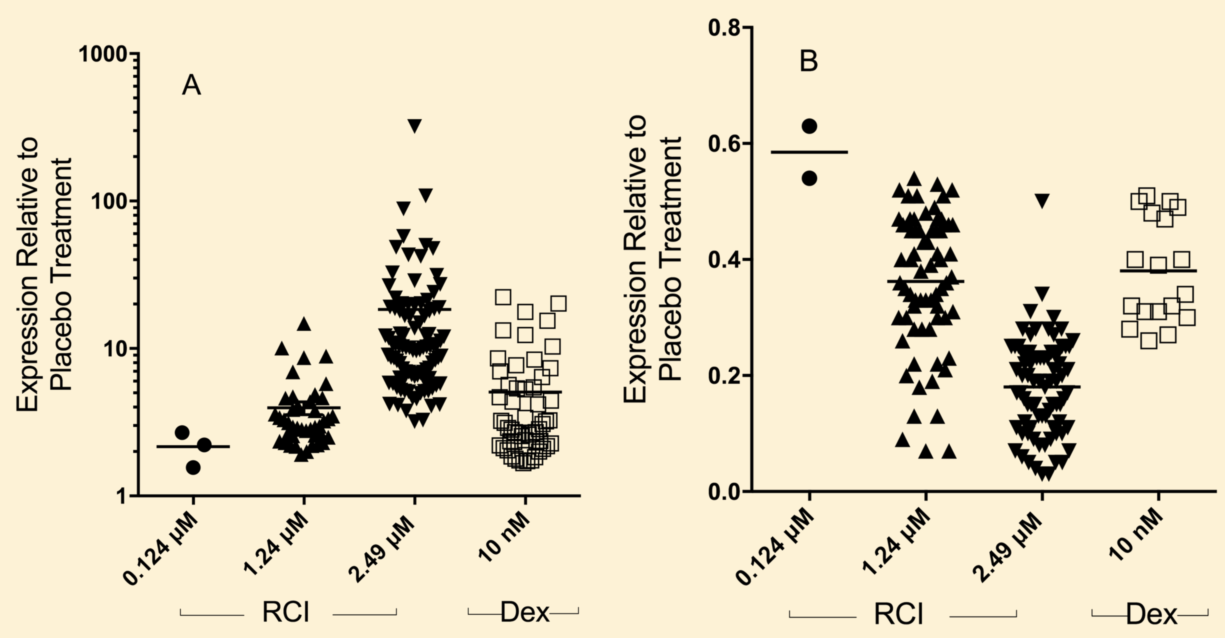

A
B
Expression Relative to Placebo Treatment
1000
100
10
1
0.8
0.6
0.4
0.2
0.0
0.124 µM
1.24 µM
2.49 µM
10 nM
RCI
Dex

Figure 1: Dose-dependent effects on gene expression in IL4/CD40L-activated human B cells resulting from treatment with RCI or Dex. Data are shown as expression relative to levels observed in cells treated with respective placebo. A) Transcripts up regulated by RCI or Dex at concentrations as shown. (B.) Transcripts downregulated by RCI or Dex at concentrations as shown.

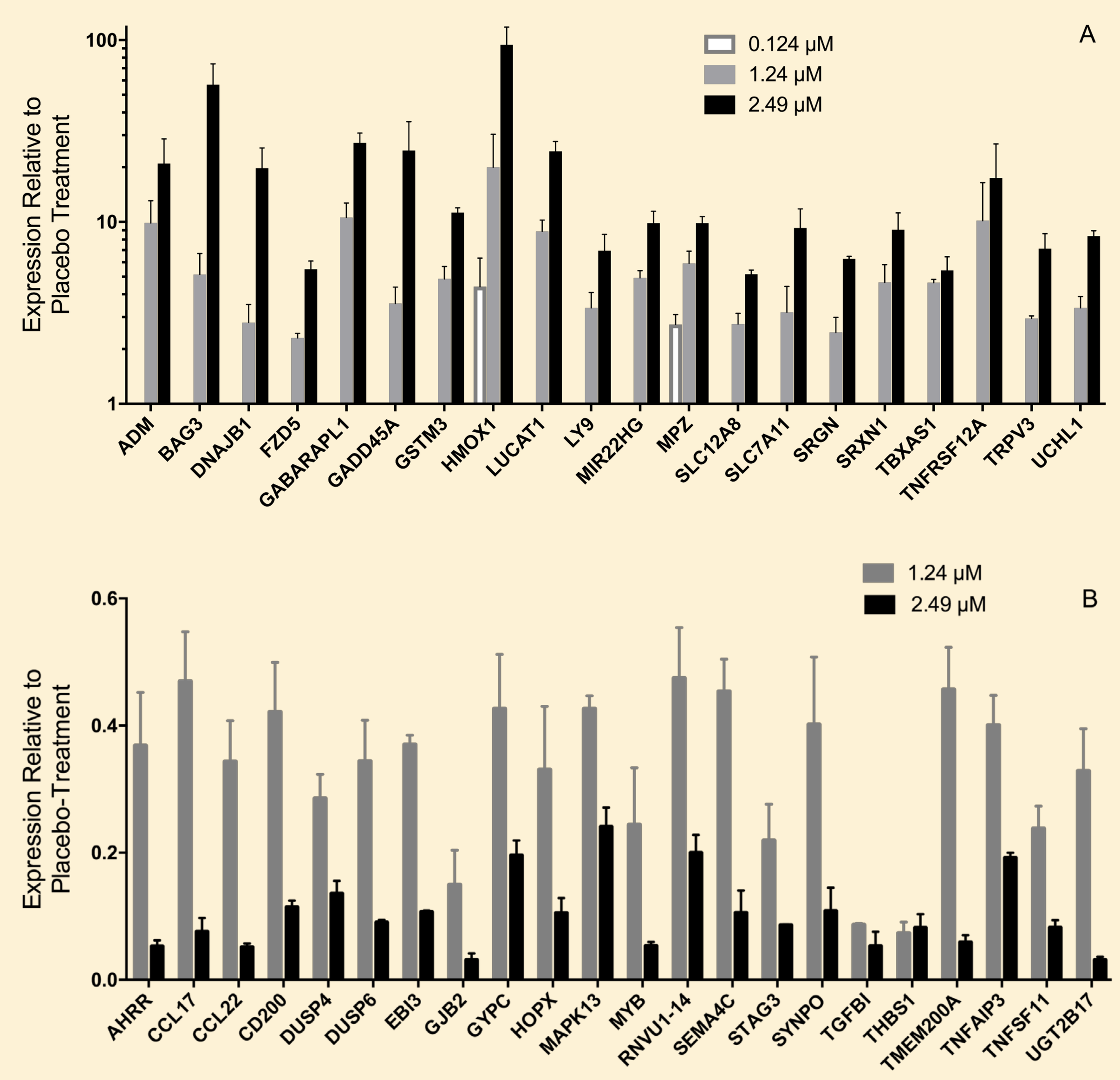

A
0.124 µM
1.24 µM
2.49 µM
Expression Relative to Placebo Treatment
100
10
1
ADM BAG3 DNAJB1 FZD5 GABARAPL1 GADD45A GSTM3 HMOX1 LUCAT1 LY9 MIR22HG MPZ SLC12A8 SLC7A11 SRGN SRXN1 TBXAS1 TNFRSF12A TRPV3 UCHL1
B
1.24 µM
2.49 µM
Expression Relative to Placebo-Treatment
0.6
0.4
0.2
0.0
AHRR CCL17 CCL22 CD200 DUSP4 DUSP6 EBI3 GJB2 GYPC HOPX MAPK13 MYB RNVU1-14 SEMA4C STAG3 SYNPO TGFBI THBS1 TMEM200A TNFAIP3 TNFSF11 UGT2B17

Figure 2. Dose-response relationships for mRNAs modulated by RCI in IL4/CD40 ligand-activated human B lymphocytes. Mean ± SEM for three RNA-Seq expts.

A) Expression relative to the level observed in placebo gel–treated cells for mRNA transcripts that were increased by treatment with RCI doses of 0.124 µM, 1.24 µM, and 2.49 µM.
B) Expression relative to level in placebo gel–treated cells for mRNA transcripts that were decreased by treatment with 1.24 µM and 2.49 µM RCI.

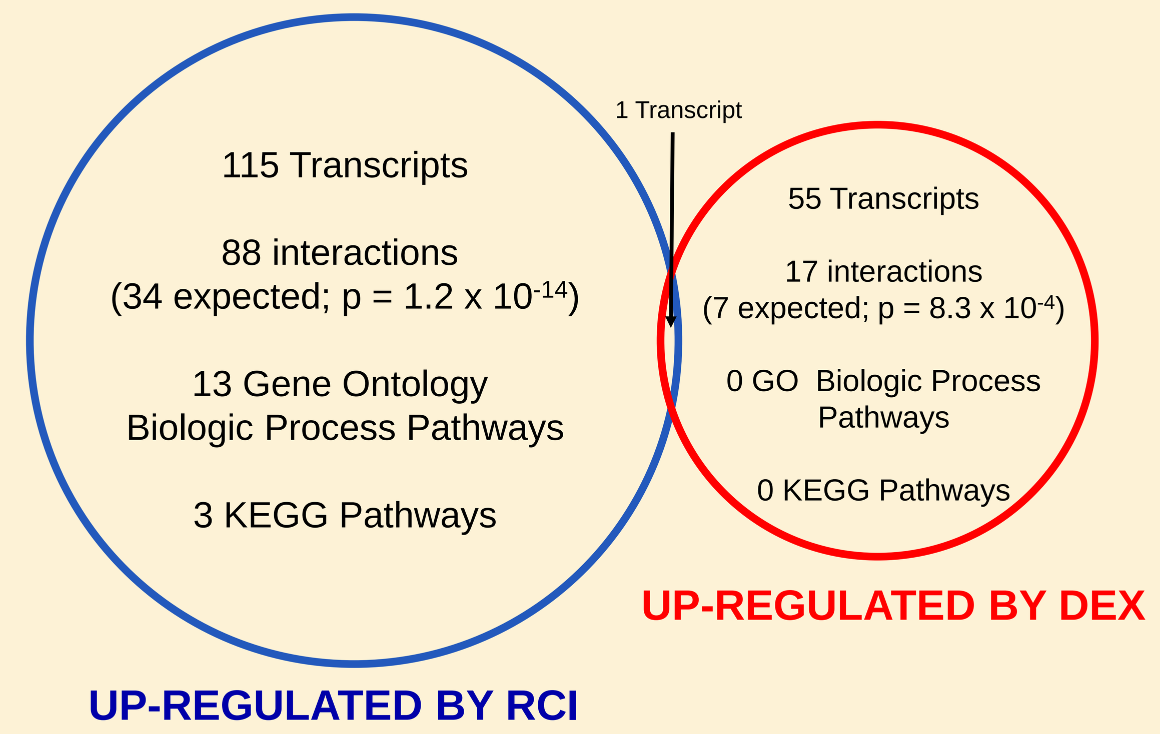

1 Transcript
115 Transcripts
88 interactions
(34 expected; p = 1.2 x 10^{-14})
13 Gene Ontology
Biologic Process Pathways
3 KEGG Pathways
55 Transcripts
17 interactions
(7 expected; p = 8.3 x 10^{-4})
0 GO Biologic Process Pathways
0 KEGG Pathways
UP-REGULATED BY DEX
UP-REGULATED BY RCI

Figure 3: STRING network analysis of mRNAs upregulated by RCI or Dex in IL4/CD40L-activated B cells cultured for 19-24 hrs. Shown are (1) the total number of transcripts upregulated, (2) the number of interactions among the encoded proteins identified by STRING from experimental and curated databases, (3) the number of GO Biologic Process Pathways found to be significantly over-represented in the regulated gene set, and (4) the number of KEGG pathways found to be significantly over-represented in the regulated gene set. Only one mRNA, encoding glutathione-S-transferase µ3 (GSTM3), was upregulated in both RCI- and Dex-treated B cells.

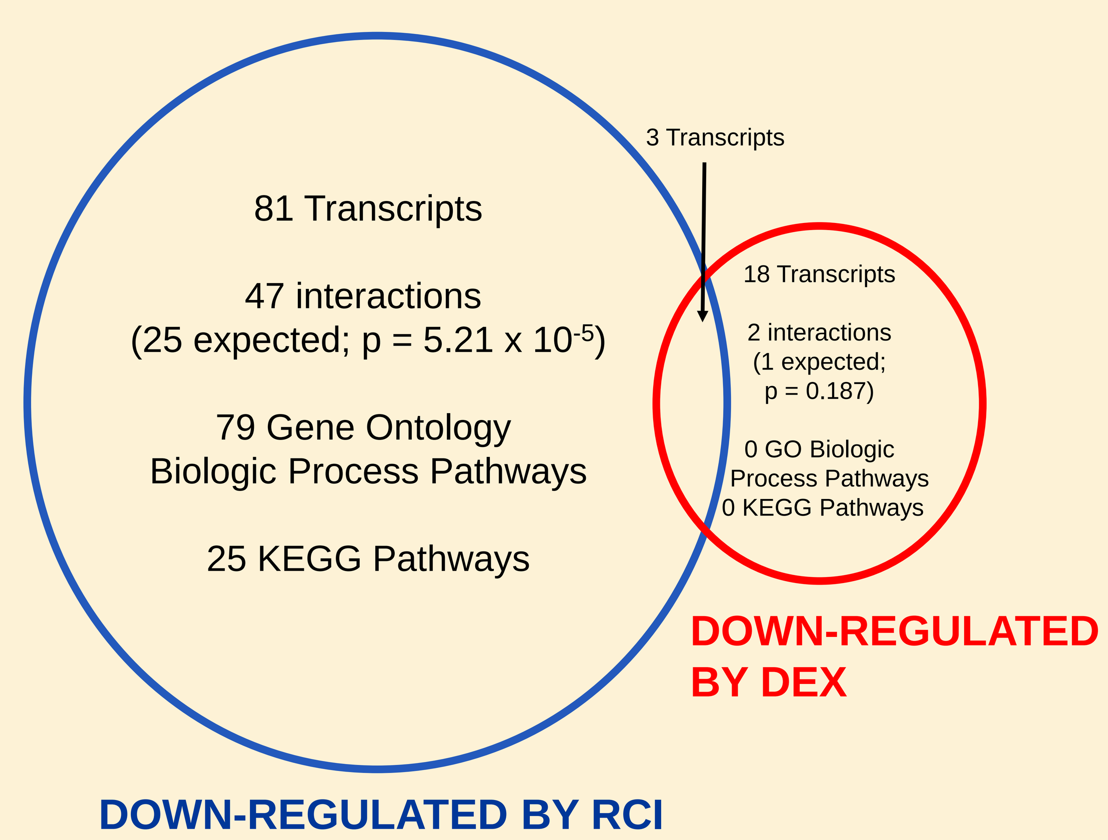

3 Transcripts
81 Transcripts
47 interactions
(25 expected; p = 5.21 x 10^{-5})
79 Gene Ontology
Biologic Process Pathways
25 KEGG Pathways
18 Transcripts
2 interactions
(1 expected;
p = 0.187)
0 GO Biologic
Process Pathways
0 KEGG Pathways
DOWN-REGULATED BY DEX
DOWN-REGULATED BY RCI

Figure 4: STRING network analysis of mRNAs downregulated by RCI or Dex in IL4/CD40L-activated human B cells in culture at 19-24 hours. Data are presented as in Figure 3. Only three mRNAs (MACROD2, PARM1, and TNFSF11) were downregulated in both RCI- and Dex-treated B cells.

Conclusions

These experiments identify specific mRNAs that are modulated by RCI treatment during B cell activation by IL4 and CD40 ligand in vitro.

- Our findings confirm that RCI exerts effects directly on mRNA expression in human B cells under glucocorticoid-free conditions.
- We found only negligible overlap between the sets of human B cell mRNAs whose levels were modulated by RCI action and those that were modulated by glucocorticoid action.
- We show that specific biologic pathways of B cell function are significantly altered by RCI treatment, and that these pathways are distinct from any modulated by the action of glucocorticoids.

References

1. Baram, TZ, et al., 1996. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics 97:375.
2. Berkovich, R, et al., 2014 Mechanisms of action of ACTH in the management of relapsing forms of multiple sclerosis. *Ther Adv Neurol Disord 7:83.*
3. Olsen, NJ, et al., 2015. Direct effects of HP Acthar Gel on human B lymphocyte activation in vitro. *Arthritis Res. Ther.* 17: 300.
4. Szklarczyk, D, et al., 2017. The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. *Nucl Acids Res*. 45:D362

Acknowledgements

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Health Care Resource Utilization and Costs for Sarcoidosis in a Commercially Insured US Population

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BACKGROUND/PURPOSE

Sarcoidosis is a multisystem inflammatory disorder characterized by granulomas (clumps of immune system cells), usually in the lungs but sometimes in other organs.

- Patients with sarcoidosis have a lower quality of life and a higher risk of comorbidities (e.g., lung disease, skin disorders, and cardiac complications).
- This study estimated the health care resource utilization and costs (direct health care costs and indirect work-loss costs) of sarcoidosis to commercial payers.

METHODS

Data source

- De-identified health care utilization records from OptumHealth Care Solutions, LLC, for more than 19.1 million beneficiaries with commercial insurance from 84 Fortune 500 companies

Definitions

- **Study period:** January 1, 1998, to March 31, 2015
- **Index date:**
 - Sarcoidosis patients: Date of earliest sarcoidosis diagnosis
 - Control group: Date of a randomly selected medical claim
- **Baseline period:** 12 months before index date
- **Outcome period:** 12 months after index date

Sample

- **Sarcoidosis group:** Patients with at least one diagnosis of sarcoidosis during the study period
- **Control group:** Patients with no sarcoidosis diagnosis during the study period
- **Both groups:** Aged 18–64 on the index date
- **Matching:** Each patient in the sarcoidosis cohort matched to a patient in the control cohort with the same Charlson Comorbidity Index (composite measure of health status), availability of work-loss data, and propensity score

Outcomes measured

- Health care resource use and costs (assessed from the payer perspective)
- Indirect work-loss costs (estimated for patients with disability information available)
- Sarcoidosis-related clinical characteristics

RESULTS

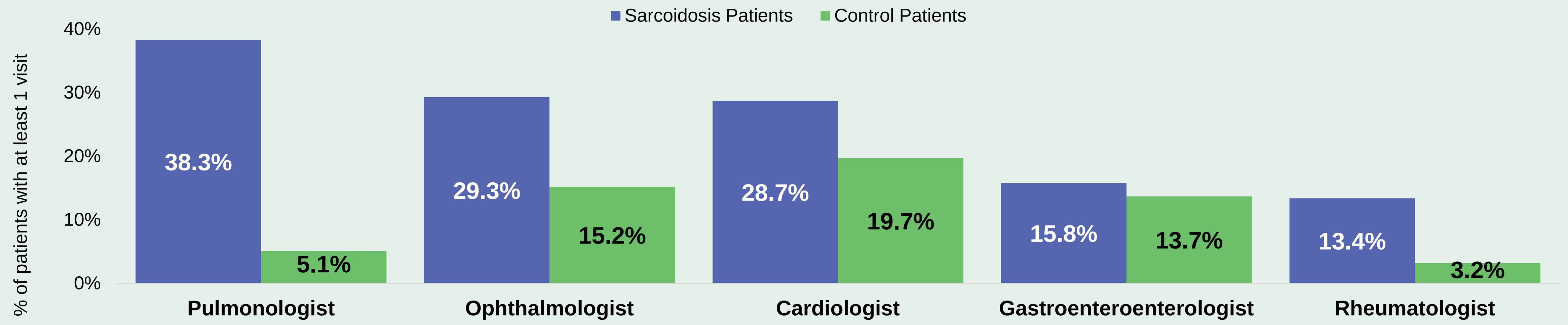
Study cohort: 7,119 patients with sarcoidosis and 7,119 matched patients in the control cohort

- After matching, the pairs of sarcoidosis and control patients had similar demographics, comorbidities, and health care utilization during the baseline period.
- Compared with controls, sarcoidosis patients had higher rates of essential (primary) hypertension (35.3% vs. 32.0%), interstitial lung disease (20.8% vs 2.5%), and uveitis (5.1% vs 0.4%).

Health care resource utilization:

- Sarcoidosis patients had 4.2 more medical visits than matched controls during the outcome period, a 22% difference.
 - Each additional visit was associated with $1,236 in additional costs.
- Sarcoidosis patients had 37% more inpatient admissions, 15% more emergency department visits, and 22% more outpatient/physician office visits than controls.
- Sarcoidosis patients were significantly more likely than controls to visit specialists (Figure 1).

Figure 1. Specialist Visits


Sarcoidosis Patients
Control Patients
% of patients with at least 1 visit
40%
30%
20%
10%
0%
38.3%
5.1%
29.3%
15.2%
28.7%
19.7%
15.8%
13.7%
13.4%
3.2%
Pulmonologist
Ophthalmologist
Cardiologist
Gastroenteroenterologist
Rheumatologist

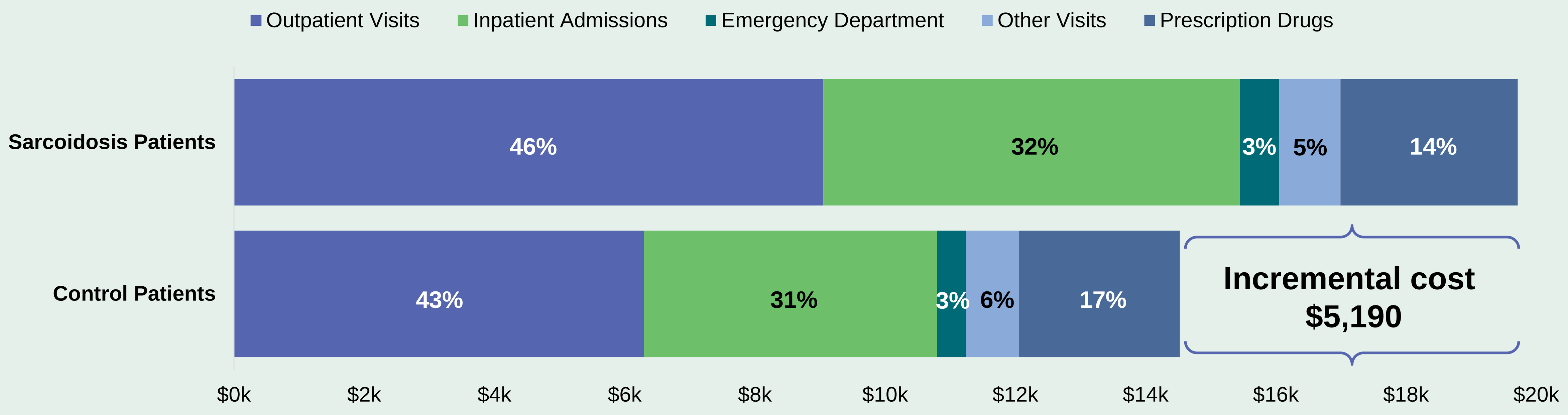
**P* < 0.001

Cost differential

Commercial payers incurred $19,714 in total annual health care costs per sarcoidosis patient during the outcome period, $5,190 (36%) more than controls (Figure 2).

- Over 50% of the additional costs were due to outpatient/physician office visits.
 - Annual cost for outpatient/ physician office visits for sarcoidosis patients: $9,050
 - Annual cost for control patients: $6,296
- Nearly 40% of the cost differential was due to inpatient admissions; each additional admission was associated with $18,980 in additional costs.

Figure 2. Total Annual Health Care Costs* Per Sarcoidosis Patient

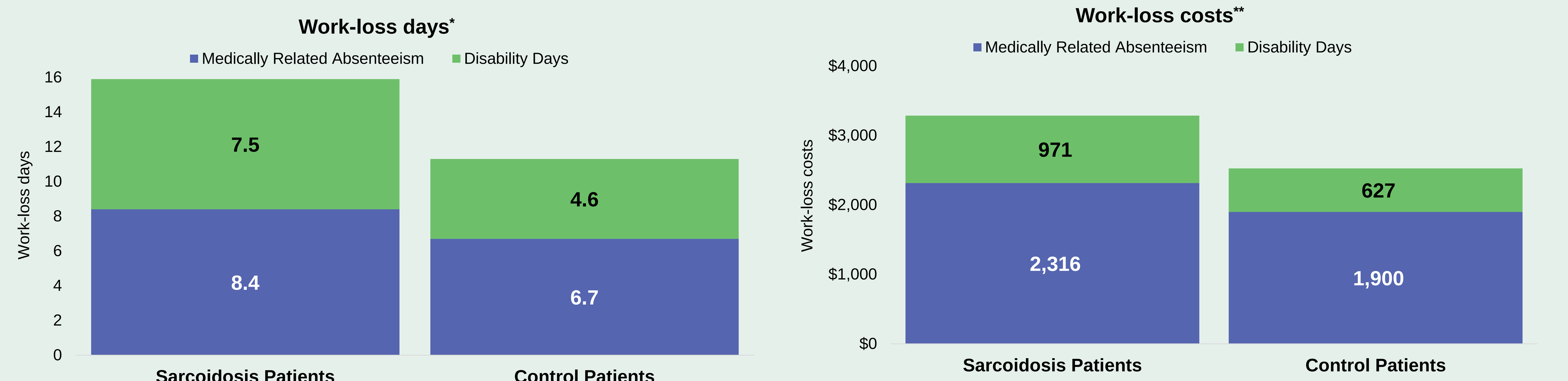

Outpatient Visits
Inpatient Admissions
Emergency Department
Other Visits
Prescription Drugs
Sarcoidosis Patients
46%
32%
3%
5%
14%
Control Patients
43%
31%
3%
6%
17%
Incremental cost
$5,190
$0k
$2k
$4k
$6k
$8k
$10k
$12k
$14k
$16k
$18k
$20k

*All comparisons significant at *P* = 0.001

RESULTS

- Sarcoidosis patients had 41% higher medical costs and 30% higher work-loss costs in the outcome period than matched controls (Figure 3).

Figure 3. Annual Medical and Work-Loss Costs Per Patient


Work-loss days*
Medically Related Absenteeism
Disability Days
Work-loss days
16
14
12
10
8
6
4
2
0
7.5
8.4
4.6
6.7
Sarcoidosis Patients
Control Patients
Work-loss costs**
Medically Related Absenteeism
Disability Days
Work-loss costs
$4,000
$3,000
$2,000
$1,000
$0
971
2,316
627
1,900
Sarcoidosis Patients
Control Patients

*Difference in work-loss days = 4.6 days (*P* = 0.001)

**Difference in work-loss costs = $761 (*P* < 0.001)

Disability and medically related absenteeism

- Sarcoidosis patients had 4.6 more days of work loss than matched controls (15.9 days vs. 11.3 days), 2.9 more disability days (7.5 vs. 4.6), and 1.8 more days of medically related absenteeism (8.4 vs. 6.7).
- Sarcoidosis patients had $3,288 in annual work-loss costs, $761 (30%) more than controls ($2,527).

Clinical Outcomes

- Sarcoidosis patients had significantly higher rates of comorbidities and prescription drug use during the outcome period than matched controls**.**

Direct and indirect burden of sarcoidosis:

- Sarcoidosis patients impose a total direct medical cost burden of up to $8.7 billion on commercial payers, or up to $2.3 billion in excess costs compared with matched controls (Figure 4).

Figure 4. Direct and Incremental Medical Burden

Total direct medical burden:

Total per-patient healthcare cost among sarcoidosis patients **$19,714 per sarcoidosis patient** × Prevalence of sarcoidosis in the US **48–330 sarcoidosis cases per 100,000 persons** × Number of adults in the US covered by commercial insurance **133.9 million persons** = **Total estimated direct medical cost burden of sarcoidosis in the US** **$1.3 –$8.7 billion**

Incremental direct medical burden:

Incremental per-patient healthcare cost (sarcoidosis minus control) **$5,190 per sarcoidosis patient** × Prevalence of sarcoidosis in the US **48–330 sarcoidosis cases per 100,000 persons** × Number of adults in the US covered by commercial insurance **133.9 million persons** = **Total incremental direct medical cost burden of sarcoidosis in the US** **$0.3 –$2.3 billion**

SUMMARY

- Sarcoidosis patients had significantly more healthcare resource utilization compared with matched controls
- The excess resource utilization among sarcoidosis patients resulted in a 36% increase in annual healthcare costs compared with matched controls
- Sarcoidosis patients in the US impose a total direct medical burden of $1.3 to $8.7 billion (in 2015$) to commercial insurers, amounting to $0.3 to $2.3 billion in excess costs over matched controls

Podium presentation at The Second International Conference on Respiratory and Pulmonary Medicine. October 17-19, 2016. Chicago, IL.

Journal publication: Rice JB, White A, Lopez A, Conway A, Wagh A, Nelson WW, Philbin M, Wan G. Economic burden of sarcoidosis in a commercially-insured population in the United States. *J Med Econ*. 2017 Jul 21:1-8. doi: 10.1080/13696998.2017.1351371. [Epub ahead of print]

Burden of Non-infectious Inflammatory Eye Diseases: A Systematic Literature Review

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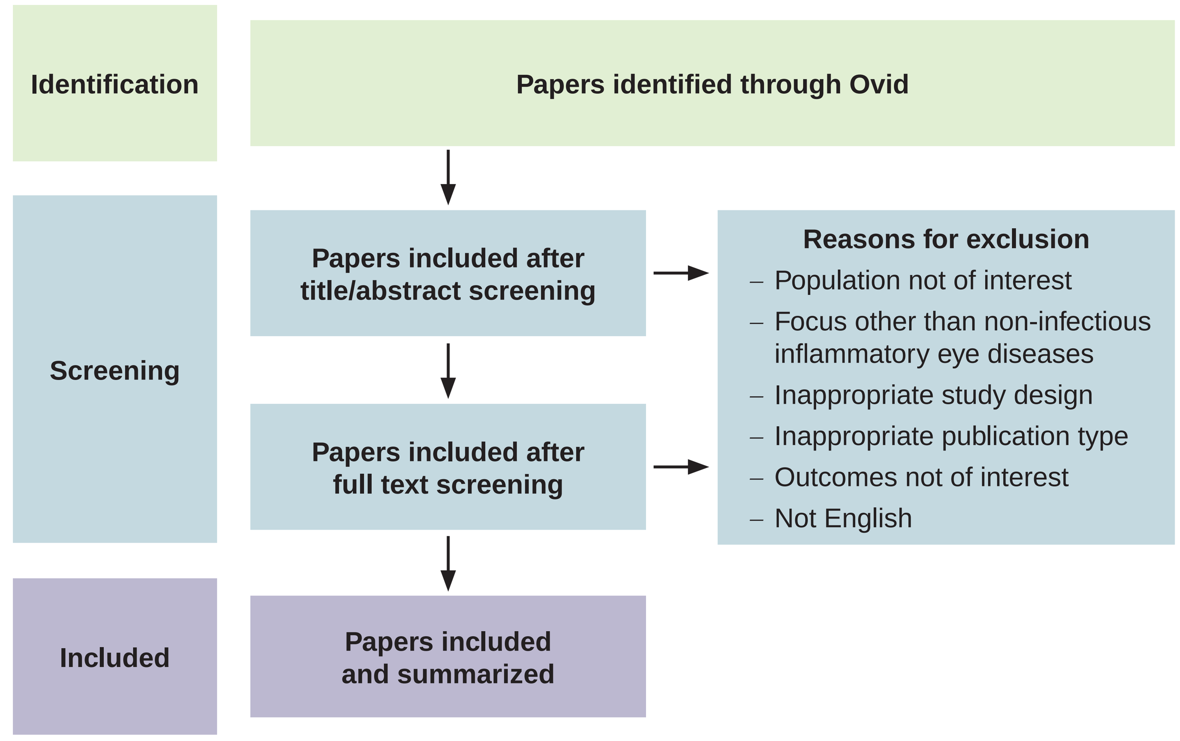
Mallinckrodt Pharmaceuticals

BACKGROUND & STUDY OBJECTIVE

- Non-infectious inflammatory eye diseases (IEDs), such as uveitis, are rare conditions with estimated incidence rates of 24.9–52.4 cases per 100,000 patient-years and annual prevalence rates of 58.0–115.3 per 100,000 patient-years[1,2]
- 10% of the over 65 population who are registered as legally blind can attribute their vision loss to IEDs and their complications[3]
- The primary goal of the treatment of IEDs is to prevent permanent vision loss
- Other treatment goals include relieving ocular pain, eliminating ocular inflammation or identifying the source of inflammation, preventing the formation of synechiae, and managing intraocular pressure[4]
- Because of the breadth of treatment options and research in recent years, the objective of this study was to conduct a systematic literature review on the burden of non-infectious inflammatory eye diseases, with a specific focus on clinical and economic outcomes to better capture the implications of IEDs and the variety of treatment options utilized

METHODS

Figure 1: Study approach


Identification
Papers identified through Ovid
Screening
Papers included after title/abstract screening
Papers included after full text screening
Reasons for exclusion
– Population not of interest
– Focus other than non-infectious inflammatory eye diseases
– Inappropriate study design
– Inappropriate publication type
– Outcomes not of interest
– Not English
Included
Papers included and summarized

NOTE: [1] The "populations not of interest" which were excluded were the pediatric population and patients with infectious eye diseases.

Literature Databases

- The Ovid search platform (Wolters Kluwer) was used to search medical and scientific databases for papers of interest
 - The Ovid platform is a commonly-used search platform for systematic literature reviews, and includes search capabilities across a range of journal articles and other publications, including those not indexed by MEDLINE
- Databases accessed through Ovid platform:
 - Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE
 - Embase
 - Cochrane Central Register of Controlled Trials
 - Cochrane Database of Systematic Reviews
 - Cochrane Methodology Register
 - Health Technology Assessment
 - NHS Economic Evaluation Database

METHODS (CONT.)

Literature Identification Criteria

Figure 2: Ovid search criteria

Non-infectious IED	Clinical trials	Clinical, medical, or economic burden
At least one of the following: "inflammatory ophthalmic disease" "inflammatory ocular disease" "inflammatory eye disease" "uveitis" "keratitis" "iritis" "iridocyclitis" "choroiditis" "optic neuritis" "chorioretinitis" "anterior segment inflammation" AND at least one of the following: "non-infectious" "autoimmune"	Ovid publication type is "uveitis adj4 trial" "clinical trial" "clinical trial, Phase I" "clinical trial, Phase II" "clinical trial, Phase III" "clinical trial, Phase IV" OR "clinical trial" in title/abstract	"complications" "clinical outcomes" "economic?" "burden" "resource utilization" "cost$" lost productivity" "disability" "medically-related absenteeism" "quality of life" "QALY?" "pharmacoeconomic?" "price$" "cost-effectiveness analysis"

Keywords:

- Paper titles/abstracts were searched to identify those with at least one keyword for non-infectious inflammatory eye disease AND represents clinical trial OR includes relevant keywords for clinical or economic outcomes

Additional criteria:

- Papers were further restricted
 - Date range: 2011–2016 for non-clinical trials; 2009–2016 for clinical trials (expanded date range to include the MUST trial)
 - Non-conference abstracts only
 - Adult humans only (i.e., papers were restricted to human subjects only and excluded if they had any of the following keyword prefixes: "pediatr$", "infant$", "child$", or "juvenile$," where $ represents a wild card)

Review Process

Reviewers:

- Titles and abstracts resulting from the literature identification criteria were assigned to two reviewers
- Reviewers worked independently and were given detailed instructions on the inclusion criteria; reviewers confirmed the initial inclusion criteria
- Upon further review of the full text, certain papers were excluded from further consideration (see below)
- Reviewers extracted information from papers based on pre-determined templates in Excel
- A project manager reviewed the extractions and worked to resolve inconsistencies, if any

Inclusion criteria:

- Focus of the paper on non-infectious inflammatory eye diseases
- Appropriate study designs (exclude papers with N < 40)
- Papers other than non-systematic reviews without expert opinions, conference abstracts, or abstracts published without an accompanying full-text article
- Focus of paper on clinical outcomes, economic outcomes, or medical resources utilization
- English only

RESULTS

Summary Statistics

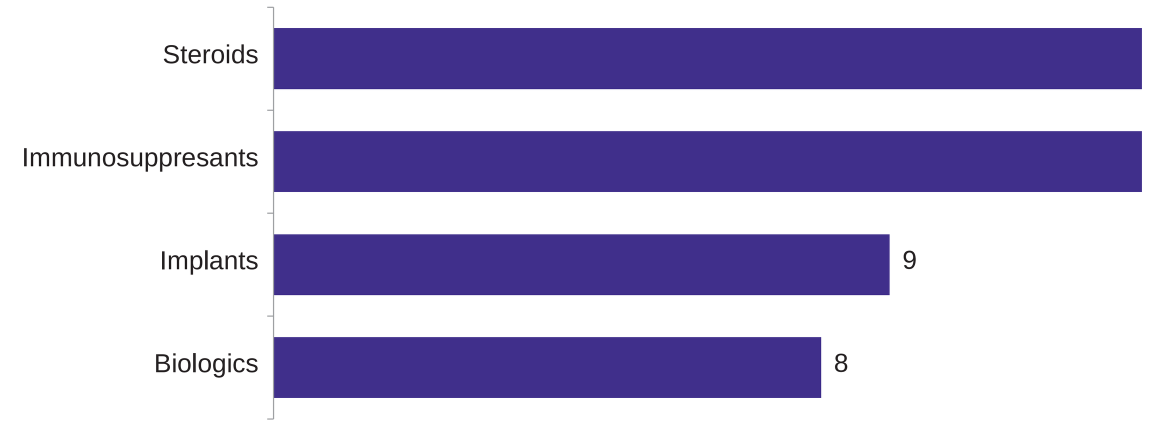
- Of the 39 papers extracted, the study designs were as follow: 21 clinical trials, 7 retrospective database analyses, 6 literature reviews, 3 chart reviews, and 2 patient surveys

Figure 3: Paper counts

	No. of papers remaining
Unique results from Ovid search	288
Exclusion criteria	
Population not of-interest	54
Focus other than non-infectious inflammatory eye diseases	58
Inappropriate study design	53
Inappropriate publication type	78
Outcomes not of interest	6
Non-English	0
Final count of papers extracted	**39**

NOTE: Papers were excluded sequentially following these criteria. The above counts reflect both the title/abstract screen and the full-text screen.

Figure 4: Types of treatment options examined for non-infectious inflammatory eye diseases


Steroids
Immunosuppresants
Implants
9
Biologics
8

NOTES:
[1] Counts reflect papers meeting inclusion criteria following both title/abstract review and full-text review.
[2] Papers reviewing multiple treatment options are included multiple times in the counts above. The "steroids" category includes both systemic and injected steroids.
[3] Examples of immunosuppressants studied in the final selection of papers include azathioprine, cyclosporine-A, and cyclophosphamide; examples of biologics include infliximab and adalimumab.

Key Themes

General research focus of included articles	▶ Cost and comparative effectiveness of newer treatments for the various types of IEDs ▶ Clinical outcomes among patients with IEDs generally, as well as IED patients receiving specific therapies ▶ Treatment options assessed include implants and systemic treatments (steroids, immunosuppressants, biologics)
Clinical findings	▶ Studies with steroid therapies report numerous negative clinical findings ▶ Non-steroid therapies may be associated with improvements in ocular comorbidities, which may result in lower health care costs and reductions in health care resource use
Economic findings	▶ The majority of economic papers assess the cost or comparative effectiveness of treatment options, as well as outcomes among patients with IEDs following specific treatments ▶ Very few papers assess the economic burden of IEDs broadly; three papers assessing the economic impact of IEDs find significant costs to the payers

RESULTS (CONT.)

Treatment Options for Non-infectious Inflammatory Eye Diseases

- Systemic treatments (immunomodulators, biologics, and/or oral corticosteroids) are generally considered effective at treating inflammation associated with IEDs[5]
- Corticosteroids are typically used as the first-line drug of choice, however, IED patients treated with corticosteroids had a significantly higher level of diagnoses of glaucoma, cystoid macular degeneration, and retinal detachments following initiation of treatment and the literature suggests that patients are not appropriately treated[6]
- Patients whose inflammation is not controlled with corticosteroids, often turn to immunosuppressants as a "steroid-sparing" therapy. These drugs have been shown to be effective at controlling inflammation, but many ophthalmologists are reluctant to use immunosuppressants due to other perceived risks (especially in younger patients), including potentially increased cancer risk and safety concerns during pregnancy and the postpartum period[7]
- There is a general consensus against using biologics as a first-line treatment,[8] due to high costs ($13,000–$20,000/year) and a perceived lack of efficacy and safety evidence[9]
- Finally, implants represent a technological advancement relative to systemic treatments, but give rise to numerous additional considerations
 - Increased rates of adverse events relative to systemic steroids in some patients (including cataracts, elevated intraocular pressure, glaucoma)[11]
 - Large upfront costs, but potentially lower maintenance costs over time, as projected by an economic model, despite higher rates of adverse events[10]
 - Given the increased risk of adverse events, patients with implants require "close monitoring" which can increase the costs of outpatient visits[11]
 - Adverse events associated with implants included costly (surgical) procedures/treatments[13]

Clinical Outcomes: Common Adverse Events

Figure 5: Common adverse events

Outcomes / adverse event	# of papers	Prevalence range
Glaucoma/elevated intraocular pressure	31	3%–65%
Cataracts	17	2%–91%
Retinal detachment	6	11%
Endophthalmitis	5	1%–5%
Hypotony	4	2%
Hypertension	4	Not reported
Hyperglycemia	2	25%
Ocular hypertension	2	12%–28%
Decrease in visual acuity	2	Not reported
Arthralgia	2	Not reported

- IED treatment, in particular corticosteroids, is associated with numerous adverse events (AEs), with frequently-cited AEs including glaucoma, elevated intraocular pressure, cataracts, and retinal detachment
- The large variation in the risk of the above adverse effects is attributable to the differences across papers in study populations, therapies, and study designs

RESULTS (CONT.)

Economic Outcomes

Figure 6: IED Economic Outcomes

Economic Outcomes
Among privately insured patients, average cost for non-infectious uveitis patients was between $13,728 to $32,268 in 2009 dollars (or, $16,302 to $38,318 in 2016 dollars), or 3.1 to 8.3 times the costs of an average patient[6]
Inpatient admissions were 83% higher for patients receiving corticosteroid treatment than those receiving therapy with biologics, 44 vs. 24 admissions per month per 1000 patients[6]
Healthcare costs for patients with non-infectious intermediate, posterior or panuveitis are 3.5 to 5.1 times those of matched controls without the conditions[12]
Implants up-front cost was $22,700 to $43,100 during first 6 months), compared to $7,700 to $8,100 with systemic therapies[10]
Implants were associated with increased rates of adverse ocular events compared to systemic corticosteroids, including cataract surgery (80% vs. 31%) and intraocular pressure-lowering surgery (26% vs. 4%)[13]

- The general consensus among these papers was that, within relatively narrowly-defined disease areas, the adverse effects associated with chronic steroid use may be costly
 - These findings have been documented for selected disease areas (e.g., panuveitis, posterior uveitis[6]), yet the literature is silent on the economic burden of non-infectious inflammatory eye diseases more broadly

CONCLUSIONS & IMPLICATIONS

- Inflammatory eye diseases (IED) are rare conditions that threaten a patient's vision
- The literature confirms that there is a considerable economic burden associated IEDs
 - Health care cost of IED patients 3 to 8 times higher than an average patient
 - Inpatient admissions were 83% higher for corticosteroid treatment than biologics
- IED treatment, in particular corticosteroids, had many of the same adverse ocular outcomes that treatments are supposed to prevent
- AE rates of different corticosteroid administrations may differ tremendously
 - 4 out of 5 steroid implant patients had cataract surgery after 2 years; 3 times the risk of systemic steroids
 - 1 out of 4 steroid implant patients had intraocular pressure-lowering surgery after 2 years; 8 times the risk of systemic steroids
- Despite ocular AEs, long-term corticosteroid use remains common, indicating that providers may not be intensifying therapy appropriately

REFERENCES

1. Acharya NR et al., *JAMA Ophthalmology,* 2013.
2. Gritz DC and Wong IG, *Ophthalmology,* 2004.
3. McCluskey et al., *BMJ,* 2000.
4. American Optometric Association, 1994.
5. Gui et al., *Ocular Immunology and Inflammation,* 2015.
6. Chu et al., *Journal of Ophthalmic Inflammation and Infection,* 2013.
7. Shaw, *American Academy of Ophthalmology,* 2011.
8. Heo et al., *Expert Opinion on Biological Therapy,* 2012.
9. Kheir et al., *Expert Review of Ophthalmology,* 2016.
10. Sugar et al., *Ophthalmology,* 2014.
11. Parekh et al., *JAMA Ophthalmology,* 2015.
12. Thorne et al., *Acta Ophthalmologica,* 2016.
13. Kempen et al., *Ophthalmology* 2011
14. Yu T et al., *Investigative Ophthalmology and Visual Science,* 2015.

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2280

Effects of Repository Corticotropin Injection on Medication Use in Patients with Rheumatologic Conditions: A Claims Data Study

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ABSTRACT

▶ **Background/Purpose**: Repository corticotropin injection (RCI) may produce anti-inflammatory and immune-modulatory effects. This study examined the demographics of patients who used RCI and the trends in medication use, specifically prednisone, after RCI initiation.

▶ **Methods**: This retrospective analysis of the Symphony Health Solutions Patient Transactional Dataset from 2008 to 2015 included patients with at least 1 claim for RA, SLE, or DM/PM, and any use of RCI. Patients with claims for non-rheumatologic conditions that may also be treated by RCI, namely, multiple sclerosis and proteinuria, were excluded. Demographics, patterns of RCI use, and concomitant medications (corticosteroids [CS], biologics, NSAIDs, and DMARDs) were reported. Patients were followed for concomitant medication use from 2 years prior to and 1 year after RCI initiation. Paired two-tailed t-tests were used to calculate the p values for the use of each drug class before/after RCI initiation.

▶ **Results**: Out of 2.7 million rheumatologic patients in the database over 6 years, there were 2,749 patients who used RCI – 1,269 RA patients, 874 SLE patients, and 606 with DM/PM (Table 1). SLE patients were younger than RA and DM/PM patients, and most of the patients were female for all 3 conditions. The majority of patients received 80U of RCI twice weekly. The study identified 504 RA, 322 SLE, and 222 DM/PM patients with sufficient follow up time to evaluate concomitant medication use. For all 3 conditions, the proportions of patients who used any CS were significantly lower after RCI initiation: reduced from 67% pre-index to 54% post-index for RA, from 73% to 58% for SLE, and from 76% to 58% for DM/PM ($p < 0.05$ for all comparisons, Figure 1). Proportions of patients on biologics and DMARDs were also significantly lowered after RCI initiation. In Figure 2, among patients who had taken CS consistently 24 weeks before RCI initiation, dose reductions were statistically significant for RA (28%), and trended lower without statistical significance for SLE (25%) and DM/PM (25%). Limitations of the retrospective analysis include uncertainties in diagnosis, medication use, and factors influencing medication changes.

▶ **Conclusion**: This claims-based study of patients with RA, SLE, and DM/PM indicated that RCI use may be associated with significant reductions in CS requirements.

BACKGROUND/PURPOSE

▶ RCI works by stimulating the adrenal cortex to secrete cortisol, corticosterone, and aldosterone[1]. Additionally, it has been shown that RCI binds to and activates all five known melanocortin receptors (MCRs)[2]. Thus, RCI may produce anti-inflammatory and immuno-modulatory effects by directly activating MCRs.

▶ The purpose of this study was to analyze prescription use patterns in patients with rheumatologic conditions and to examine the trends of concomitant medication use, especially prednisone, after RCI administration.

METHODS

Study Design and Data Source

▶ This study used data from the Symphony Health Solutions claims database, which captures health events in 17 out of every 20 persons in the U.S. with any insurance types, including Medicare and Medicaid.

▶ Pediatric and adult patients newly initiated on RCI were included in the analysis if they had at least one claim for the following International Classification of Disease, Ninth Revision (ICD-9) diagnosis codes:

- RA (ICD-9 code 714.0, 714.30, 714.31, 714.32, 714.33)
- SLE (ICD-9 code 710.0)
- DM (ICD-9 code 710.3), and PM (ICD-9 code 710.4)

▶ Patient characteristics were reported for the overall study population

▶ A subset of patients were followed longitudinally to study medication use patterns. Those with insurance claims two years prior to the first RCI use and one year after the last RCI use were included.

Statistical Analysis

▶ Paired two-tailed t-tests examined the use of CS, biologics, NSAIDs, and DMARDs during 6 months before and 6 months after RCI initiation. The mean prednisone dose pre-RCI and post-RCI was compared among patients who received prednisone prior to RCI initiation.

RESULTS

Table 1. Patient Characteristics of the Overall Population

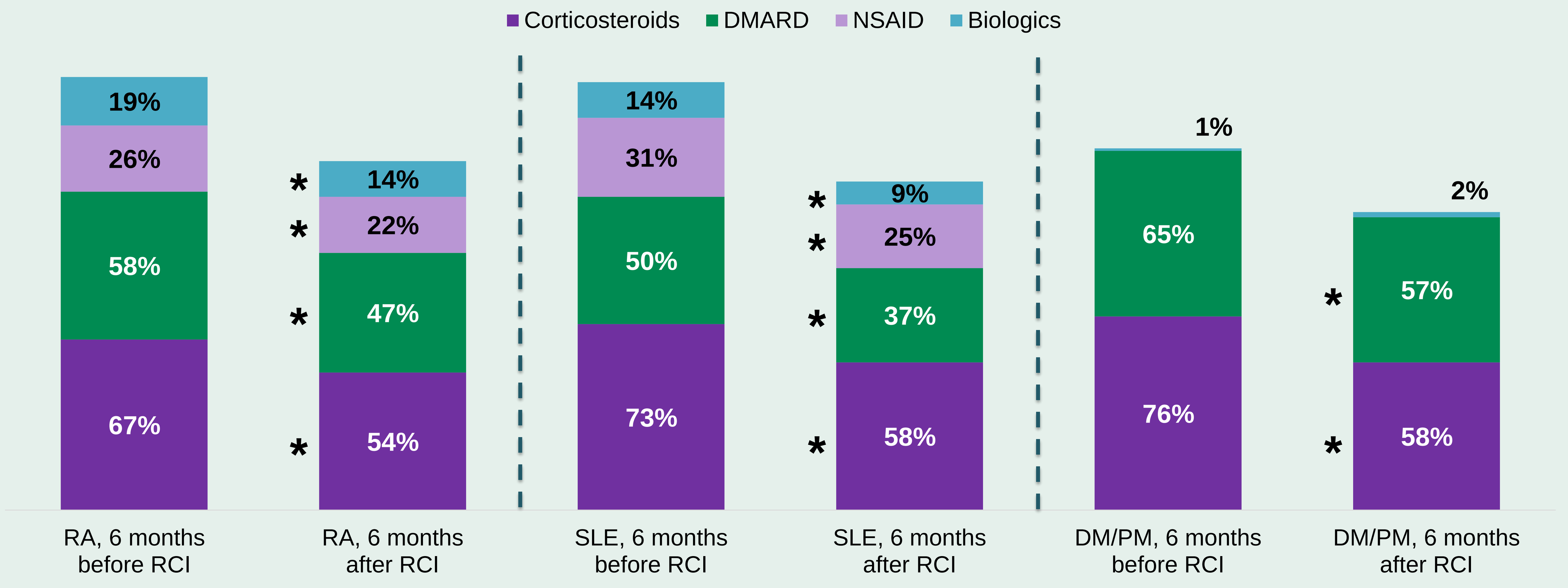
Patient Characteristics	RA	SLE	DM/PM
Number of patients on RCI	1,269	874	606
Age, Mean (Years)	59.1	48.1	55.5
Female	78%	89%	70%
RCI dose of 80U twice weekly	58%	57%	68%
RCI dose of 200U weekly	12%	15%	16%
RCI duration, Mean (Days)	115.7	129.2	157.1

▶ From the overall population, there was a subset of 504 RA, 322 SLE, and 222 DM/PM patients evaluated for the use of biologics, NSAIDs, DMARDs, and CS before and after RCI use.

▶ The proportion of patients on prednisone after RCI use decreased from 67% of patients to 54% for RA, 73% to 58% for SLE, and 76% to 58% for DM/PM. The declines were significant for all three disease groups, as indicated by p value <0.05 (Figure 1).

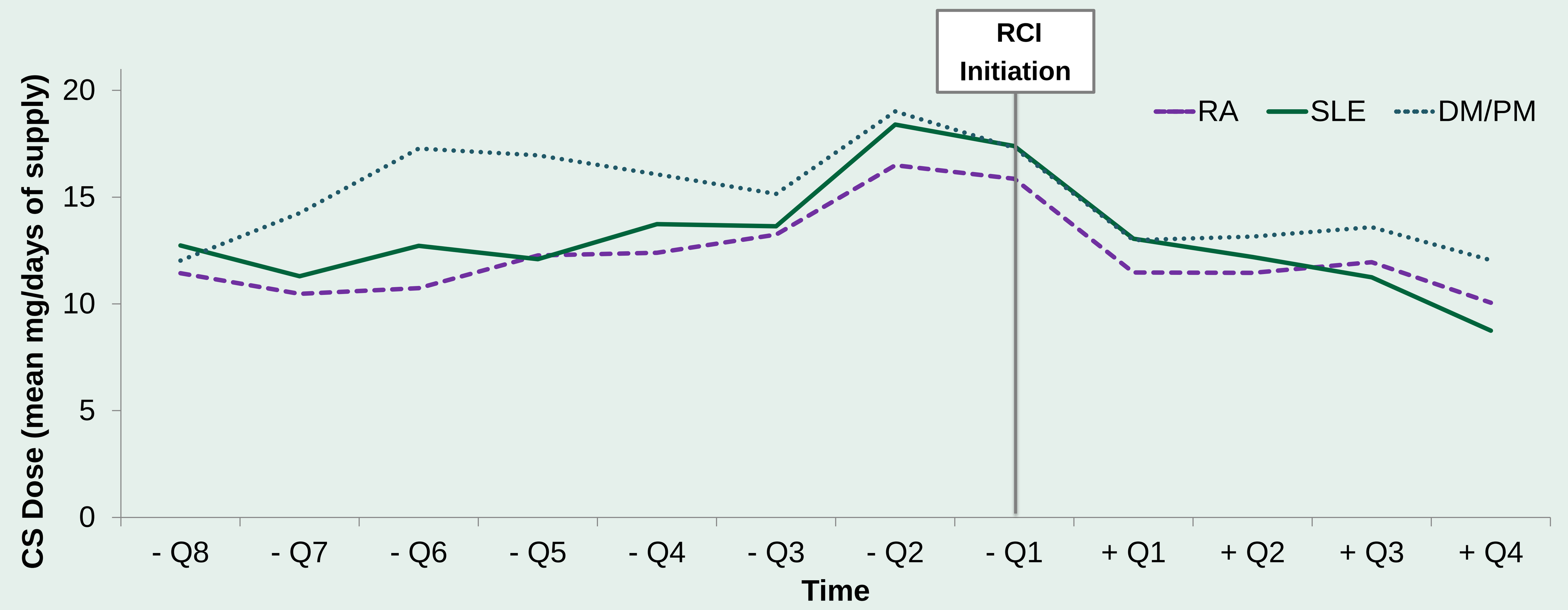
▶ The use of NSAIDs, DMARDs, and biologics decreased significantly in RA and SLE patients. The use of DMARDs decreased significantly in DM/PM patients (Figure 1).

Figure 1. Medication Use Before and After Repository Corticotropin Injection (RCI) Initiation


Corticosteroids
DMARD
NSAID
Biologics
19%
26%
58%
67%
14%
22%
47%
54%
14%
31%
50%
73%
9%
25%
37%
58%
1%
65%
76%
2%
57%
58%
RA, 6 months before RCI
RA, 6 months after RCI
SLE, 6 months before RCI
SLE, 6 months after RCI
DM/PM, 6 months before RCI
DM/PM, 6 months after RCI

* denotes p<0.05. Sum of column >100% because patients received multiple medications concomitantly

Figure 2. Corticosteroid (CS) Dose Trends in Patients who had 24 weeks of Consistent Use before Repository Corticotropin Injection (RCI) Initiation


RCI Initiation
RA
SLE
DM/PM
CS Dose (mean mg/days of supply)
20
15
10
5
0
- Q8
- Q7
- Q6
- Q5
- Q4
- Q3
- Q2
- Q1
+ Q1
+ Q2
+ Q3
+ Q4
Time

	RA	SLE	DM/PM
Number of patients	**201**	**131**	**121**
CS Dose 1Q Pre-RCI, Mean ± 95% CI	**15.86** ± 1.71	**17.39** ± 2.27	**17.31** ± 2.18
CS Dose 1Q Post-RCI, Mean ± 95% CI	**11.47** ± 1.63	**13.05** ± 2.27	**12.98** ± 2.34

RESULTS

▶ Among RA patients who had taken prednisone consistently 24 weeks before RCI use, the mean prednisone dose significantly decreased by 28% at 12 weeks (or 1 quarter) after RCI initiation (15.86 ± 1.71 mg per day to 11.47 ± 1.63mg per day) (Figure 2).

▶ In SLE and DM/PM, the mean prednisone dose trended lower with 25% reductions but without statistical significance (Figure 2).

LIMITATIONS

▶ Factors such as co-morbidities and disease activities might have influenced medication changes.
▶ Diagnoses and medication use were derived from information in outpatient, institutional, and pharmacy claims. As a result, no information was available on the diagnostic certainty or disease activity.
▶ No information was available on clinical consequences of decreases in concomitant medication use after RCI administration.
▶ Further prospective study will be needed to address disease activities during and after RCI use and to determine clinical impact of reduction in prednisone use.

CONCLUSION

▶ This claims-based study indicates that RCI use might reduce the use of prednisone, DMARDs, and biologics. Further prospective study is needed to determine the impact of such reductions.

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DISCLOSURE

▶ Study funding was provided by Mallinckrodt Pharmaceuticals. Data Analysis was performed by Mallinckrodt Pharmaceuticals.

REFERENCES

1. Gettig J, Cummings JP, and Matuszewski K. H.P. Acthar Gel and Cosyntropin Review. *Pharmacy and Therapeutics* 2009;34:250-257
2. Gong R. Leveraging melanocortin pathways to treat glomerular diseases. *Adv Chronic Kidney Dis*. 2014;21(2):134–151

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A Multicenter, Randomized, Parallel-Group, Double-blind, Multiple-Dose, Placebo-Controlled Study to Assess the Efficacy and Safety of MNK-1411 in Male Subjects 4 to 8 Years of Age With Duchenne Muscular Dystrophy (DMD)

Mallinckrodt Pharmaceuticals

Background

- DMD is an X chromosome–linked disease that causes progressive muscle loss and leads to symptomatic cardiomyopathy and respiratory failure, which both contribute to the associated mortality[1,2]
- Corticosteroids (mainly prednisone and deflazacort) are the only medications to date that have demonstrated broad efficacy on a variety of functional endpoints in randomized, placebo-controlled clinical studies of patients with DMD[3-5]
- MNK-1411 is a long-acting formulation of cosyntropin acetate, a synthetic 24–amino acid adrenocorticotropic hormone (ACTH1-24) analogue
- It is hypothesized that MNK-1411 may delay DMD progression by activating melanocortin receptors to reduce inflammation and attenuate muscle damage and by stimulating endogenous cortisol release[6-9]
- In a single-center, open-label, PK/PD, and safety study in healthy adult volunteers, IM and SC doses of MNK-1411 were well tolerated, and adverse events were consistent with the safety profile of long-acting cosyntropin products marketed outside the United States

Purpose

- The purpose of this study is to evaluate the effects of MNK-1411 in patients with DMD

Objectives

- The primary objective of this study is to determine the effect of MNK-1411 on motor function in subjects with DMD
- Secondary objectives include assessing the effect of MNK-1411 on additional measures of motor function and muscle strength and determining the safety and tolerability of MNK-1411 in patients with DMD



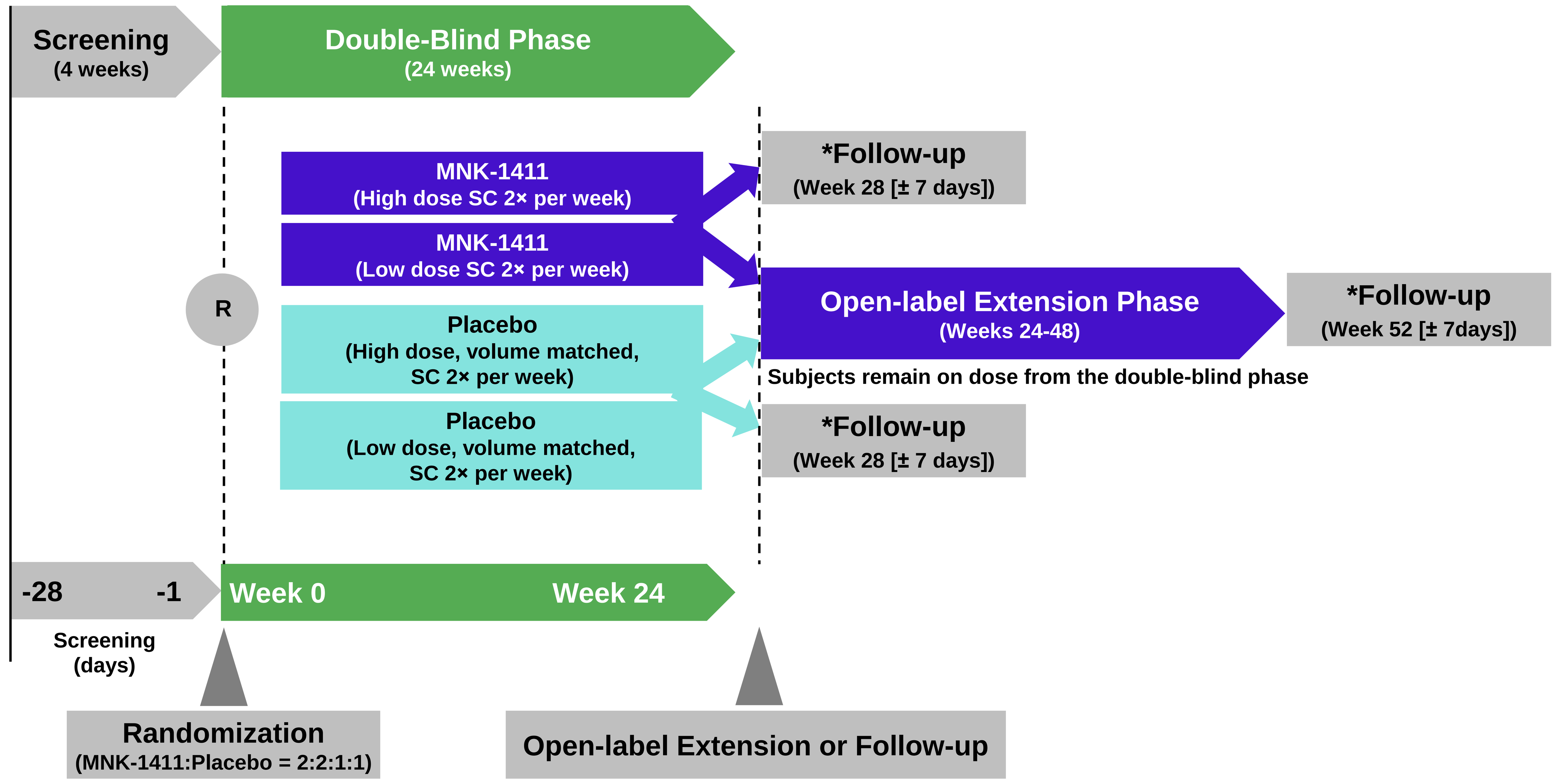
Image Source: EasyStand. https://www.flickr.com/photos/easystand/4921292690/in/photostream/. Accessed August 21, 2017.

Study Population

- Males, 4 to 8 years of age (inclusive)
- DMD diagnosis confirmed by
 - Complete dystrophin deficiency
 - Identifiable DMD gene mutation
 - Complete dystrophin gene sequencing consistent with DMD
 - Clinical profile

Study Design

- Anticipated enrollment: ~132 subjects



Screening
(4 weeks)
Double-Blind Phase
(24 weeks)
MNK-1411
(High dose SC 2× per week)
MNK-1411
(Low dose SC 2× per week)
R
Placebo
(High dose, volume matched, SC 2× per week)
Placebo
(Low dose, volume matched, SC 2× per week)
*Follow-up
(Week 28 [± 7 days])
Open-label Extension Phase
(Weeks 24-48)
*Follow-up
(Week 52 [± 7days])
Subjects remain on dose from the double-blind phase
*Follow-up
(Week 28 [± 7 days])
-28
-1
Week 0
Week 24
Screening
(days)
Randomization
(MNK-1411:Placebo = 2:2:1:1)
Open-label Extension or Follow-up

*All subjects will have a follow-up visit at 28 (±7) days after their last dose of study drug. Subjects who complete the study and do not enter the open-label extension will have their follow-up visit at approximately Week 28. Subjects who complete the open-label extension will have their follow-up visit at approximately Week 52.

Study Endpoints

Primary Endpoint

- Change from baseline in the 10-meter walk/run test at Week 24

Secondary Endpoints

- Change from baseline in North Star Ambulatory Assessment, 4-stair climb, time to stand from supine, and quantitative muscle testing at Week 24
- General safety profile, including adverse events, vital signs, immunogenicity, and laboratory assessments over the entire study

References

1. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010;9(1):77-93.
2. McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other clinical endpoints in Duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. *Muscle Nerve*. 2013;48(3):357-368.
3. Fenichel GM, Florence JM, Pestronk A, et al. Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. *Neurology*. 1991;41(12):1874-1877.
4. Griggs RC, Moxley RT 3rd, Mendell FR, et al. Prednisone in Duchenne dystrophy. A randomized, controlled trial defining the time course and dose response. Clinical Investigation of Duchenne Dystrophy Group. *Arch Neurol*. 1991;48(4):383-388.
5. Mendell JR, Moxley RT, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. *N Engl J Med.* 1989;320(24):1592-1597.
6. Catania A, Gatti S, Colombo G, Lipton JM. Targeting melanocortin receptors as a novel strategy to control inflammation. *Pharmacol Rev*. 2004;56(1):1-29.
7. Lam CW, Perretti M, Getting SJ. Melanocortin receptor signaling in RAW264.7 macrophage cell line. *Peptides*. 2006;27(2):404-412.
8. Cossu G, Cusella-De Angelis MG, Senni MI, et al. Adrenocorticotropin is a specific mitogen for mammalian myogenic cells. *Dev Biol*. 1989;131(2):331-336.
9. Xia Y, Wikberg JE. Localization of ACTH receptor mRNA by in situ hybridization in mouse adrenal gland. *Cell Tissue Res.* 1996;286(1):63-68.

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Abbreviations: IM, intramuscular; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; TEAE, treatment-emergent adverse event.