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Pharmacokinetics and Pharmacodynamics of Repository Corticotropin Injection Compared With Synthetic ACTH$_{1\text{-}24}$ Depot and Methylprednisolone in Healthy Subjects

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Abstract

Repository corticotropin injection (RCI; Acthar Gel) is a naturally sourced complex mixture of adrenocorticotropic hormone (ACTH) analogs and other pituitary peptides. This phase 1, single-center, open-label, randomized parallel study directly compared the pharmacokinetics and pharmacodynamics of RCI and synthetic ACTH$_{1\text{-}24}$ depot. Methylprednisolone was included to estimate the steroidogenic exposure of RCI and synthetic ACTH$_{1\text{-}24}$ depot when used to treat nephrotic syndrome. A total of 48 healthy subjects aged 18 to 50 years were randomly assigned 1:1:1 to RCI (80 IU subcutaneously twice weekly on study days 1 and 4), synthetic ACTH$_{1\text{-}24}$ depot (1 mg subcutaneously twice weekly on study days 1 and 4), or methylprednisolone (32 mg orally once daily on study days 1 through 6). After 2 doses, RCI induced about 5-fold lower free cortisol exposure and an estimated 4-fold lower steroidogenic exposure than synthetic ACTH$_{1\text{-}24}$ depot. The lower endogenous cortisol response of RCI was achieved despite higher observed mean plasma concentrations of N25-deamidated porcine ACTH$_{1\text{-}39}$ (the pharmacokinetic marker for RCI) than of ACTH$_{1\text{-}24}$. The different pharmacodynamic properties demonstrated by RCI and synthetic ACTH$_{1\text{-}24}$ depot in this study suggest that these products in the ACTH class are not interchangeable.

Keywords

pharmacodynamics, pharmacokinetics, RCI, repository corticotropin injection, synthetic ACTH$_{1\text{-}24}$ depot

Inflammatory disorders lead to debilitating tissue damage, causing significant morbidity and impaired quality of life.[1] Patients with these disorders demonstrate variable responses to standard-of-care treatments, which include nonsteroidal anti-inflammatory drugs, biologics, disease-modifying therapies, and immunosuppressants.[2] Corticosteroids are used for short-term management of disease flares or as second-line alternatives for inflammation.[3]

Corticosteroids mimic the activity of endogenous cortisol, affecting most metabolic processes in the body.[3,4] As a result, corticosteroids have extensive adverse effects that include changes in blood pressure and blood glucose, electrolyte disturbances, edema, poor wound healing, muscle wasting, osteoporosis, immunosuppression, thromboembolism, and drug-related Cushing syndrome.[3,5] About 30% of patients who use corticosteroids will become resistant to their efficacy as a result of prolonged treatment or disease progression.[6,7] Thus, alternative therapies that promote an anti-inflammatory response while minimizing changes in cortisol exposure are needed, particularly for patients in whom there is a poor clinical response to corticosteroids or those who are unable to tolerate their side effects.

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Repository corticotropin injection (RCI; Acthar Gel) has demonstrated therapeutic benefit for persistent inflammatory disorders and other conditions that have exhibited an inadequate response to corticosteroids and standard-of-care treatments.[8–18] RCI is approved by the US Food and Drug Administration for the treatment of infantile spasms and various allergic, autoimmune, inflammatory, and rheumatic diseases. Historically, the anti-inflammatory effects of RCI were thought to be due to its induction of endogenous cortisol through activation of melanocortin receptor 2 (MC2R) in the adrenal cortex; accordingly, RCI is often mistaken for adrenocorticotropic hormone (ACTH). However, results of preclinical studies suggest that RCI also induces a direct immunomodulatory effect, independent of endogenous cortisol production, by engaging MCRs 1, 3, 4, and 5 on immune cells.[19–23]

Various ACTH analogs have been shown to exhibit unique binding and functional activity at each MCR,[23–25] which may have distinct effects on endogenous cortisol production and immunologic responses. The purpose of the current study was to characterize the differences in cortisol production and to estimate the steroidogenic exposure of RCI and synthetic $ACTH_{1\text{-}24}$ depot. RCI is a naturally sourced complex mixture of ACTH analogs and other pituitary peptides that is solubilized in 16% gelatin to yield a prolonged-release formulation. A major component of the formulated complex mixture is N-25 deamidated (N25D) porcine $ACTH_{1\text{-}39}$. Synthetic $ACTH_{1\text{-}24}$ depot is a long-acting suspension that contains the first 24 amino acids of the full-length $ACTH_{1\text{-}39}$ and is complexed with zinc to prolong its release. Synthetic $ACTH_{1\text{-}24}$ depot is an investigational drug that is similar to Synacthen Depot, a product used therapeutically in other countries. Results of previous studies have suggested that RCI has less functional activity at MC2R[23] and induces a lower level of endogenous cortisol production than synthetic $ACTH_{1\text{-}24}$ depot after a single dose.[26,27] An indirect comparison of 2 independent pharmacokinetic (PK) and pharmacodynamic (PD) studies of RCI and synthetic $ACTH_{1\text{-}24}$ depot used a model-based simulation to compare clinically relevant doses of each drug and found that RCI induced lower cortisol exposure and had a lower steroidogenic exposure than synthetic $ACTH_{1\text{-}24}$ depot.[27] To further assess these findings, we conducted a direct head-to-head comparison study using RCI and synthetic $ACTH_{1\text{-}24}$ depot as reported in this article.

The current study is the first to report a direct comparison of clinically relevant doses (used for nephrotic syndrome) of RCI and synthetic $ACTH_{1\text{-}24}$ depot that assesses the differences in their cortisol production and estimated steroidogenic exposure. Oral doses of methylprednisolone used for nephrotic syndrome were used to estimate the steroidal equivalent doses of RCI and synthetic $ACTH_{1\text{-}24}$ depot. This study also characterized the PK and safety of each drug.

Methods

Study Objectives

The objectives of this study were as follows: to assess the PK of RCI, synthetic $ACTH_{1\text{-}24}$ depot, and methylprednisolone; to compare the PD of RCI with synthetic $ACTH_{1\text{-}24}$ depot; to estimate prednisone-equivalent doses of RCI and synthetic $ACTH_{1\text{-}24}$ depot; and to assess the safety of RCI, synthetic $ACTH_{1\text{-}24}$ depot, and methylprednisolone.

Subjects

The study was conducted at PRA Health Sciences, Inc. (Salt Lake City, Utah). The study protocol and informed consent forms were reviewed and approved by Midlands Independent Review Board (Overland Park, Kansas) before any subjects provided consent. Subjects gave written informed consent before the initiation of study procedures. The study complied with local and federal regulations and with ethical guidelines outlined in the Declaration of Helsinki.

Healthy subjects were included if they were aged 18 to 50 years at the screening visit; weighed >50 kg at the screening and check-in visits; had a body mass index ≥ 18.5 and ≤ 30 kg/m^2 at the screening and check-in visits; and were healthy as determined by medical history, physical examination, and clinical laboratory measurements. Subjects were excluded if they had a history of adverse or allergic reactions to any study drug or similar products; used prescription or over-the-counter oral, injected, inhaled, or topical corticosteroids within 30 days of the screening visit; recently donated or received blood products; had major surgery within 3 months or serious illness requiring hospitalization within 6 months of the check-in visit; had current or recent cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, infectious, musculoskeletal, neurologic, psychiatric, pulmonary, or renal disorders; or had current or recent alcohol, drug, or nicotine abuse.

Study Design

This phase 1, single-center, open-label, randomized, parallel group study assigned 48 subjects to 1 of 3 study drugs (Figure 1): 16 subjects received RCI 80 IU subcutaneously (SC) twice weekly on study days 1 and 4; 16 subjects received synthetic $ACTH_{1\text{-}24}$ depot 1 mg SC twice weekly on study days 1 and 4; and 16 subjects received oral methylprednisolone 32 mg (two 16-mg

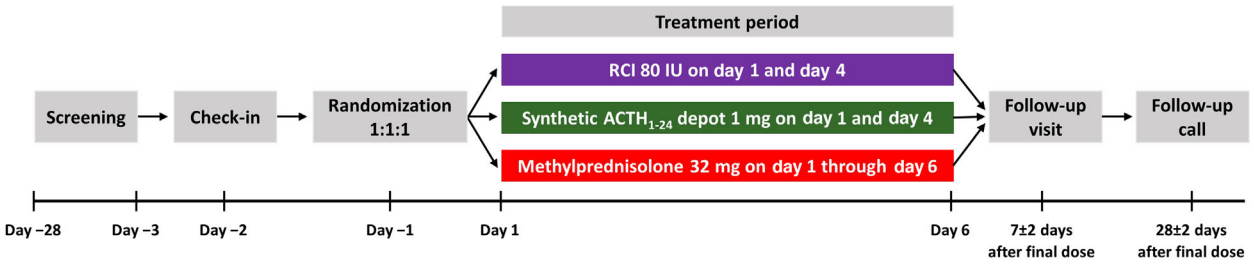

Figure 1. Study design. $ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; RCI, repository corticotropin injection.

tablets) once daily on study days 1 through 6. All subjects completed the study. Baseline demographics were collected during the screening period between study day −28 and day −3. Subjects remained at the clinic from 2 days before the first dose of the study drug (day −2) until study day 8.

Oral methylprednisolone is a corticosteroid commonly used for the treatment of inflammatory disorders such as nephrotic syndrome.[28] Methylprednisolone was included in this study to determine its steroidogenic exposure and for estimation of the prednisone dose equivalence of RCI and synthetic $ACTH_{1-24}$ depot when used at clinically relevant doses. Therefore, the dosing regimens for RCI and methylprednisolone in this study were chosen to match the typical maintenance doses for each drug when used to treat nephrotic syndrome.[8,12,28] The dosing regimen for synthetic $ACTH_{1-24}$ depot was chosen to match the maintenance dose of the Synacthen Depot product used outside of the United States for nephrotic syndrome.[28]

Analytical Methods

Serum samples for total cortisol and plasma samples for free cortisol, total methylprednisolone, free methylprednisolone, and $ACTH_{1-24}$ were analyzed by Syneos Health (Quebec City, Quebec, Canada); plasma samples for N25D porcine $ACTH_{1-39}$ were analyzed by QPS Netherlands BV (Groningen, Netherlands). Concentrations for all analytes were determined using liquid chromatography–tandem mass spectrometry methods that were validated according to the US Food and Drug Administration Bioanalytical Method Validation Guidance (May 2018). Details of the validated bioanalytical methods for all analytes can be found in the Supplemental Information.

Pharmacokinetic Analyses

Serial whole blood samples were drawn from each subject over 24 hours after RCI, synthetic $ACTH_{1-24}$ depot, and methylprednisolone administration on study day 1 and day 4 for determination of plasma concentrations of N25D porcine $ACTH_{1-39}$ (a major component of the complex mixture of RCI), $ACTH_{1-24}$, and total and free methylprednisolone, respectively. All subjects whose PK profile contained at least 4 consecutive quantifiable concentrations were included in the PK population. Further details regarding PK analyses for all 3 study drugs can be found in the Supplemental Information.

Pharmacodynamic Analyses

Plasma Free and Serum Total Cortisol. Whole blood samples were drawn from each subject at predefined time points after RCI, synthetic $ACTH_{1-24}$ depot, and methylprednisolone administration and were time-matched on study day −1, day 1, and day 4 for determination of plasma free and serum total cortisol concentrations. All subjects whose PD profile contained at least 4 consecutive quantifiable concentrations of total and free cortisol on both day −1 and day 1 were included in the PD population.

The following PD parameters for plasma free and serum total cortisol were estimated for RCI and synthetic $ACTH_{1-24}$ depot: maximum effect at 24 hours and 48 hours (E_{max24} and E_{max48}, respectively); time to E_{max24} and E_{max48} (TE_{max24} and TE_{max48}, respectively); area under the effect curve for the concentration-time profile from time zero to 24 hours and to 48 hours ($AUEC_{24}$ and $AUEC_{48}$, respectively); and baseline-corrected values for each (E_{max24}[BA], E_{max48}[BA], TE_{max24}[BA], TE_{max48}[BA], $AUEC_{24}$[BA], and $AUEC_{48}$[BA], respectively). $AUEC_{24}$[BA] and $AUEC_{48}$[BA] for day 1 and day 4 were calculated by subtracting the $AUEC_{24}$ and $AUEC_{48}$ on day −1 from the respective day 1 and day 4 estimates for each study drug. $AUEC_{24}$[BA] and $AUEC_{48}$[BA] for serum total and plasma free cortisol after administration of synthetic $ACTH_{1-24}$ depot were compared to $AUEC_{24}$[BA] and $AUEC_{48}$[BA] for total and free cortisol after administration of RCI, respectively.

PD parameters were estimated using actual blood collection times by noncompartmental methods using Phoenix WinNonlin 8.1 (Certara USA, Inc., Princeton, New Jersey). $AUEC_{24}$ and $AUEC_{48}$ were calculated using the linear trapezoidal with linear interpolation rule.

Steroidogenic Exposure. Whole blood samples were drawn from each subject at predefined time points over 24 hours after oral methylprednisolone administration

on study days 1 and 4 for determination of plasma total and free methylprednisolone concentrations. All subjects who were in both the PK and PD populations were included in the steroidogenic exposure population.

Because oral methylprednisolone is known to suppress endogenous cortisol production,[29] PD parameters for serum total and plasma free cortisol after administration of methylprednisolone were not calculated. Instead, the steroidogenic concentration (CSG) of methylprednisolone was estimated. As a corticosteroid, methylprednisolone exhibits systemic action similar to cortisol; therefore, the CSG of methylprednisolone took into account the effects arising from endogenous cortisol ($Conc_{Cortisol}$) and from methylprednisolone itself. Additionally, methylprednisolone is considered 5 times more potent than cortisol (ie, every 1 mg of methylprednisolone is equivalent to 5 mg of cortisol).[4] Therefore, a conversion factor of 5 was applied to the methylprednisolone concentration ($Conc_{MPD}$).[30] The following equation was used to estimate the CSG of methylprednisolone:

$$CSG = (5 \times Conc_{MPD}) + Conc_{Cortisol}$$

CSG was used to estimate the following PD parameters for the steroidogenic concentration of plasma total and free methylprednisolone: maximum observed effect for the CSG concentration-time profile (E_{maxSG}), time of E_{maxSG} (T_{maxSG}), and area under the effect curve for the CSG concentration-time profile from time 0 to 24 hours ($AUEC_{24SG}$). Baseline-corrected $AUEC_{24SG}$ ($AUEC_{24SG}$[BA]) was calculated by subtracting the baseline (day −1) cortisol concentrations from the time-matched day 1 CSG.

Estimated Prednisone-Equivalent Doses. To estimate the prednisone equivalence of the studied doses of RCI and synthetic $ACTH_{1\text{-}24}$ depot, we multiplied the plasma free cortisol $AUEC_{24}$[BA] on day 4 for RCI and synthetic $ACTH_{1\text{-}24}$ depot by 2 (the number of weekly doses of each drug).

This value was divided by the free cortisol $AUEC_{24SG}$[BA] on day 4 for 32 mg of methylprednisolone, then multiplied by the dose of methylprednisolone (32 mg). The prednisone-equivalent dose was then calculated by multiplying this value by 1.25 (ie, every 1 mg of methylprednisolone is equivalent to 1.25 mg of prednisone) as provided in the equation below:

Prednisone-equivalent dose =

[(Day 4 free cortisol $AUEC_{24}$ [BA] × 2)/

(Day 4 free cortisol $AUEC_{24SG}$[BA])] × 32 mg × 1.25

Safety Analyses

All subjects who received at least 1 dose of the study drug were in the safety population. Safety was assessed via adverse events (AEs), treatment-emergent AEs (TEAEs; events that occurred after the first dose of study drug and through study completion), serious TEAEs (TESAEs), physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory test findings collected throughout the study.

Statistical Analyses

All PK parameters, PD parameters, and safety results were summarized descriptively. For plasma free and serum total cortisol exposure, the changes from baseline in $AUEC_{24}$ and $AUEC_{48}$ after administration of RCI and synthetic $ACTH_{1\text{-}24}$ depot were compared using an analysis of variance. The analysis of variance model, with study drug as a fixed effect and subject as a random effect, was performed on days 1 and 4 for $AUEC_{24}$[BA] and $AUEC_{48}$[BA] after natural log (ln) transformation. The results were back-transformed to the original scale. The ratio (percentage) of geometric least squares means, corresponding 90% confidence intervals, and *P* values are presented.

Results

Subjects

Baseline subject demographics are presented in Table 1. Subjects were predominantly men (75.0%) and White (83.3%) and were not of Hispanic or Latino ethnicity (83.3%). The mean age, body weight, and body mass index were similar among the 3 study drug groups.

Pharmacokinetics

N-25 deamidated porcine $ACTH_{1\text{-}39}$. Plasma N25D porcine $ACTH_{1\text{-}39}$, a major component in the complex mixture of RCI, was utilized as the plasma marker. Mean plasma N25D porcine $ACTH_{1\text{-}39}$ concentrations increased rapidly following SC injection, with the mean peak N25D porcine $ACTH_{1\text{-}39}$ concentration occurring at 1 hour after the first dose (Figure 2). On day 4, the mean peak plasma N25D porcine $ACTH_{1\text{-}39}$ concentration occurred at 1 hour and was slightly lower than that observed on day 1.

The estimated PK parameters for plasma N25D porcine $ACTH_{1\text{-}39}$ are provided in Table 2. After SC administration of RCI to healthy subjects, N25D porcine $ACTH_{1\text{-}39}$ was absorbed rapidly from the injection site with a median time to maximum concentration t_{max} of 2.0 hours and 1.1 hours after single and multiple dosing, respectively. The terminal elimination half-life ($t_{\frac{1}{2}}$) could not be calculated for 6 subjects on day 1 and for 9 subjects on day 4, as 3 consecutive quantifiable concentrations were not observed after the peak

Table 1. Baseline[a] Subject Demographics

	RCI 80 IU SC Twice Weekly	Synthetic $ACTH_{1-24}$ Depot 1 mg SC Twice Weekly	Methylprednisolone Tablets 32 mg Orally Daily
	n = 16	n = 16	n = 16
Age, y, mean (SD)	29.1 (5.5)	25.9 (4.7)	27.9 (6.2)
Sex, n (%)			
Female	3 (18.8)	3 (18.3)	6 (37.5)
Male	13 (81.3)	13 (81.3)	10 (62.5)
Race, n (%)			
American Indian or Alaska Native	2 (12.5)	0	1 (6.3)
Asian	1 (6.3)	0	0
Black or African American	1 (6.3)	1 (6.3)	1 (6.3)
White	12 (75.0)	14 (87.5)	14 (87.5)
Other	0	1 (6.3)	0
Ethnicity, n (%)			
Hispanic or Latino	3 (18.8)	4 (25.0)	1 (6.3)
Not Hispanic or Latino	13 (81.3)	12 (75.0)	15 (93.8)
Weight, kg, mean (SD)	74.9 (9.7)	77.6 (12.6)	78.7 (15.2)
BMI, kg/m^2, mean (SD)	24.1 (2.4)	24.4 (3.1)	25.1 (2.9)

$ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; BMI, body mass index; RCI, repository corticotropin injection; SC, subcutaneous; SD, standard deviation.
[a] Collected during the screening period between study day −28 and day −3.

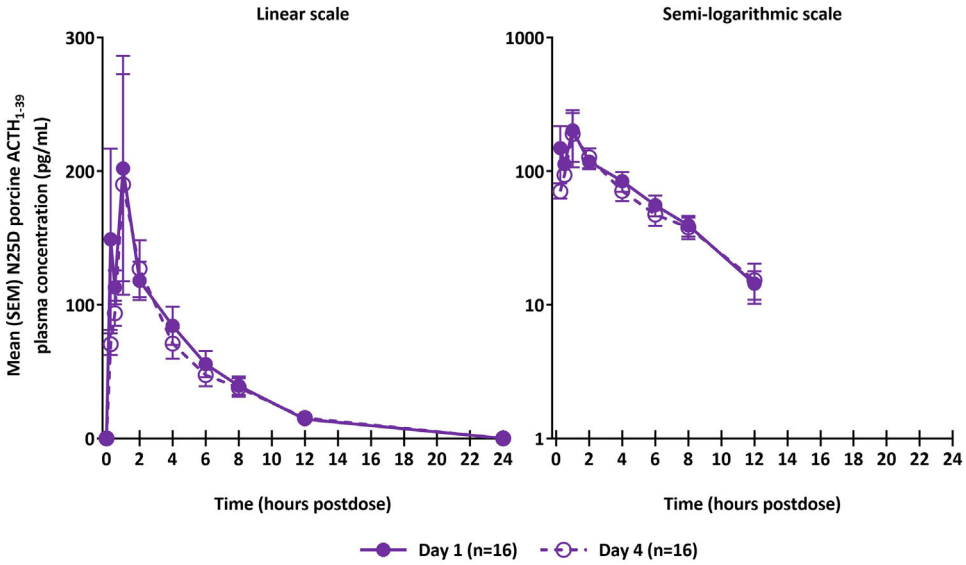

Figure 2. Mean (SEM) plasma N25D porcine $ACTH_{1-39}$ concentration-time profile on study days 1 and 4 using a linear scale (left) and a semilogarithmic scale (right). $ACTH_{1-39}$, the first 39 amino acids of adrenocorticotropic hormone; N25D, N-25 deamidated; SEM, standard error of the mean.

concentration. The mean $t_{\frac{1}{2}}$ for N25D porcine $ACTH_{1-39}$ following single- and multiple-dose administration was 2.6 hours and 3.4 hours, respectively. As quantifiable plasma N25D porcine $ACTH_{1-39}$ concentrations were not observed after 12 hours on days 1 and 4, area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}) and relative AUC from 0 to 24 hours ($RAUC_{0-24}$) were not estimated; AUC_{0-last} was reported instead of AUC_{0-24} for day 4.

Adrenocorticotropic hormone$_{1-24}$. Mean plasma $ACTH_{1-24}$ concentrations increased rapidly following SC injection, with peak concentration occurring at 15 minutes after dosing (Figure 3). The mean peak plasma $ACTH_{1-24}$ concentration on day 4 occurred at 15 minutes and was slightly lower than the mean peak $ACTH_{1-24}$ concentration observed on day 1.

The plasma PK parameters that were estimated for $ACTH_{1-24}$ are provided in Table 3. After SC

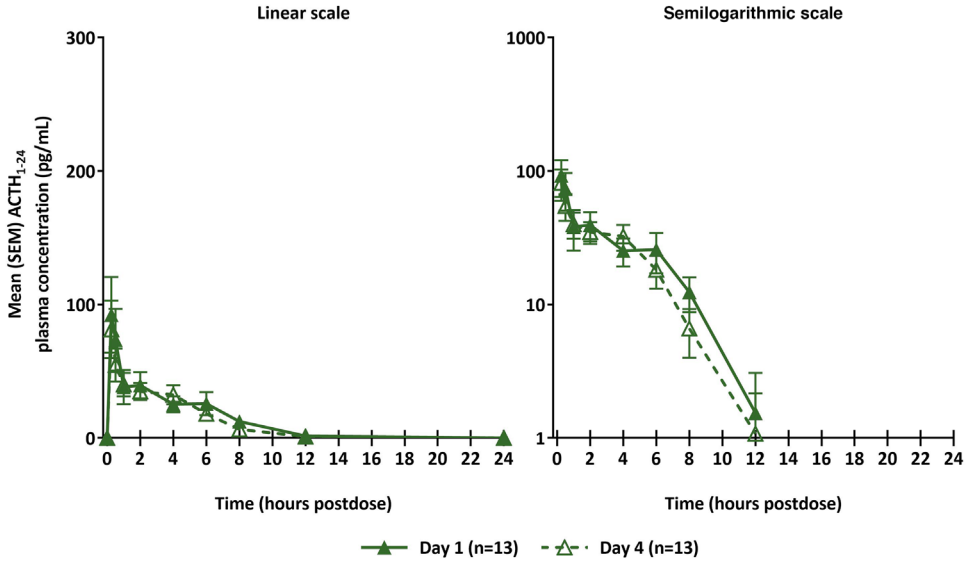

Figure 3. Mean (SEM) plasma $ACTH_{1-24}$ concentration-time profile on study days 1 and 4 using a linear scale (left) and a semilogarithmic scale (right). $ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; SEM, standard error of the mean.

Table 2. Mean (SD)[a] N25D porcine $ACTH_{1-39}$ Plasma Pharmacokinetic Parameters After Twice-Weekly Administration of RCI 80 IU SC, Study Day 1 and Day 4[b]

PK Parameter, Unit	Day 1	Day 4
C_{max}, pg/mL	n = 16	n = 16
	293.0 (401.0)	203.0 (327.0)
t_{max}, h	n = 16	n = 16
	2.0 (0.3-8.0)	1.1 (0.3-4.0)
$t_{\frac{1}{2}}$, h	n = 10	n = 7
	2.6 (0.6)	3.4 (0.6)
$AUC_{0\text{-last}}$, pg • h/mL	n = 16	n = 16
	797 (396)	722 (440)
$AUC_{0\text{-inf}}$, pg • h/mL	n = 10	NA
	1020 (406)	

$ACTH_{1-39}$, the first 39 amino acids of adrenocorticotropic hormone; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, observed peak plasma concentration; N25D, N-25 deamidated; NA, not applicable; PK, pharmacokinetic; RCI, repository corticotropin injection; SC, subcutaneously; SD, standard deviation; $t_{\frac{1}{2}}$, terminal elimination half-life; T_{max}, time of maximum observed plasma concentration.
[a] T_{max} is presented as median (minimum-maximum).
[b] PK parameters were estimated for subjects who had at least 4 consecutive quantifiable plasma concentrations for N25D porcine $ACTH_{1-39}$.

Table 3. Mean (SD)[a] $ACTH_{1-24}$ Plasma Pharmacokinetic Parameters After Twice-Weekly Administration of Synthetic $ACTH_{1-24}$ Depot 1 mg SC, Study Day 1 and Day 4[b]

PK Parameter, Unit	Day 1	Day 4
C_{max}, pg/mL	n = 13	n = 13
	103.0 (103.0)	86.1 (75.0)
t_{max}, h	n = 13	n = 13
	0.3 (0.3-6.0)	0.3 (0.3-4.0)
$AUC_{0\text{-last}}$, pg • h/mL	n = 13	n = 13
	259 (231)	227 (184)

$ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, observed peak plasma concentration; NA, not applicable; PK, pharmacokinetic; SC, subcutaneously; SD, standard deviation; t_{max}, time of maximum observed plasma concentration.
[a] T_{max} is presented as median (minimum-maximum); mean is presented when $n \geq 2$.
[b] PK parameters were estimated for subjects who had at least 4 consecutive quantifiable plasma concentrations for $ACTH_{1-24}$.

administration of synthetic $ACTH_{1-24}$ depot, $ACTH_{1-24}$ was absorbed rapidly from the injection site, with a median t_{max} of 0.3 hours after single and multiple dosing. Fourteen subjects had quantifiable concentrations for up to 8 hours, and 2 subjects had quantifiable concentrations for up to 12 hours. Except for 1 and 2 subjects on days 1 and 4, respectively, $t_{\frac{1}{2}}$ could not be calculated, as 3 consecutive quantifiable plasma $ACTH_{1-24}$ concentrations were not observed after the peak concentration. The $t_{\frac{1}{2}}$ of $ACTH_{1-24}$ following a single dose was 2.8 hours, and the mean $t_{\frac{1}{2}}$ following multiple doses was 2.8 hours. Because quantifiable plasma $ACTH_{1-24}$ concentrations were not observed after 12 hours on days 1 and 4, $AUC_{0\text{-}24}$ and $RAUC_{0\text{-}24}$ were not estimated; $AUC_{0\text{-last}}$ was reported instead of $AUC_{0\text{-}24}$ for day 4.

Plasma Total and Free Methylprednisolone. The mean plasma total methylprednisolone concentration peaked around 2 hours after oral dosing and declined rapidly (Figure 4A). On day 4, the mean plasma total methylprednisolone concentration was slightly lower than on day 1. Similar to the plasma total methylprednisolone

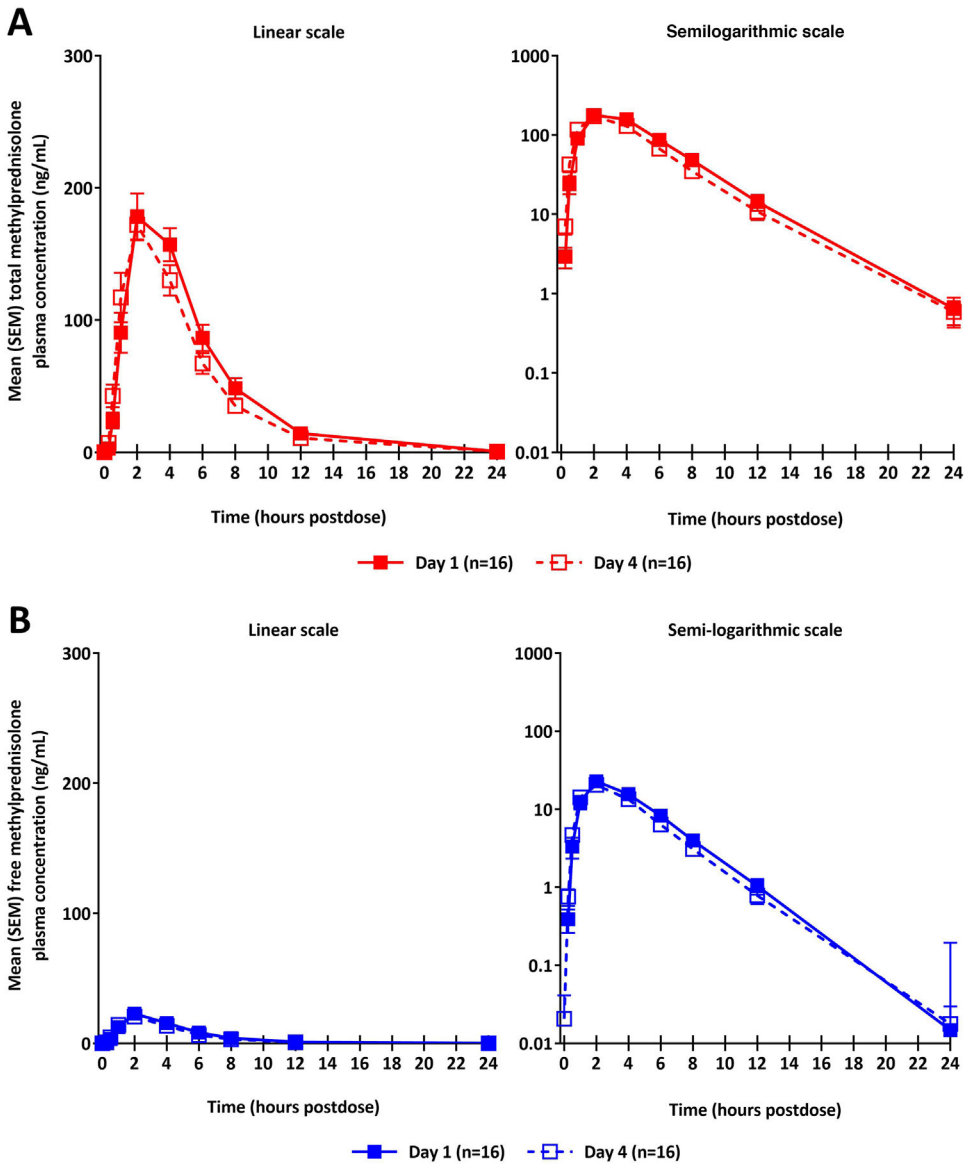

Figure 4. Mean (SEM) plasma total (A) and free methylprednisolone (B) concentration-time profiles on study days 1 and 4 using a linear scale (left) and a semilogarithmic scale (right). SEM, standard error of the mean.

concentration, the mean plasma free methylprednisolone concentration peaked at 2 hours after oral dosing and declined rapidly (Figure 4B). On day 4, the mean plasma total methylprednisolone concentration was slightly lower than on day 1.

The estimated PK parameters for plasma total and free methylprednisolone are provided in Table 4. After oral administration of methylprednisolone tablets, total methylprednisolone was absorbed with a median t_{max} of 2 hours after single and multiple doses. The mean $t_{\frac{1}{2}}$ of methylprednisolone following single and multiple doses was quite similar (2.2 hours and 2.4 hours, respectively). No accumulation of methylprednisolone was seen with mean $RAUC_{0\text{-}24}$ of 0.9. Similar to plasma total methylprednisolone, the median t_{max} for plasma free methylprednisolone was 2 hours for both day 1 and day 4. The mean $t_{\frac{1}{2}}$ for plasma free methylprednisolone (1.9 hours and 2.0 hours for day 1 and day 4, respectively) was quite similar to total methylprednisolone (2.2 hours and 2.4 hours for day 1 and day 4, respectively). The mean exposure of plasma free methylprednisolone was about 8% of the mean exposure of plasma total methylprednisolone on both days. Only 1 subject had a quantifiable plasma free methylprednisolone concentration until 24 hours after dosing. $RAUC_{0\text{-}24}$ for this subject was 0.8.

Plasma concentration-time profiles for free and total methylprednisolone and PK parameters estimated from

Table 4. Mean (SD)[a] Plasma Total and Free Methylprednisolone Pharmacokinetic Parameters After Administration of Oral Methylprednisolone 32 mg Daily, Study Day 1 and Day 4[b]

PK Parameter, Unit	Day 1	Day 4
Total methylprednisolone		
C_{max}, ng/mL	n = 16	n = 14
	198.0 (51.4)	188.0 (40.0)
t_{max}, h	n = 16	n = 14
	2.0 (2.0-4.0)	2.0 (1.0-4.0)
$t_{\frac{1}{2}}$, h	n = 16	n = 14
	2.2 (0.6)	2.4 (0.7)
$AUC_{0\text{-last}}$, ng • h/mL	n = 16	n = 14
	1020 (381)	919 (297)
$AUC_{0\text{-inf}}$, ng • h/mL	n = 16	NA
	1030 (380)	
Free methylprednisolone[b]		
C_{max}, ng/mL	n = 16	n = 15
	24.6 (7.4)	21.9 (5.4)
t_{max}, h	n = 16	n = 15
	2.0 (1.0-4.0)	2.0 (1.0-4.0)
$t_{\frac{1}{2}}$, h	n = 16	n = 13
	1.9 (0.5)	2.0 (0.5)
$AUC_{0\text{-last}}$, ng • h/mL	n = 16	n = 15
	104.0 (35.2)	89.5 (27.3)
$AUC_{0\text{-inf}}$, ng • h/mL	n = 16	NA
	106 (36)	

$AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, observed peak plasma concentration; NA, not applicable; PK, pharmacokinetic; SD, standard deviation; $t_{\frac{1}{2}}$, terminal elimination half-life; t_{max}, time of maximum observed plasma concentration.

[a] T_{max} is presented as median (minimum-maximum); mean is presented when $n \geq 2$.

[b] PK parameters were estimated for subjects who had at least 4 consecutive quantifiable plasma concentrations for total and free methylprednisolone.

these plasma concentrations were consistent with those reported in the literature.[31,32]

Pharmacodynamics

Plasma Free and Serum Total Cortisol. Because plasma free cortisol is pharmacologically active, we assessed free cortisol concentrations as an indicator of the physiologic effects of each study drug. The mean peak baseline-corrected free cortisol concentrations on study day 1 (Figure 5A) and day 4 (Figure 5B) were about 2-fold lower after administration of clinically relevant doses of RCI compared to synthetic $ACTH_{1\text{-}24}$ depot.

Following a single dose (day 1) and multiple doses (day 4) of RCI, the free cortisol concentrations returned to baseline by 24 hours after dosing, whereas free cortisol concentrations were observed for up to 48 hours after administration of synthetic $ACTH_{1\text{-}24}$ depot. The mean peak baseline-corrected serum total cortisol concentrations on study day 1 (Figure 6A) and day 4 (Figure 6B) were about 2-fold lower after administration of clinically relevant doses of RCI compared to synthetic $ACTH_{1\text{-}24}$ depot. At 24 hours after administration of RCI on both day 1 and day 4, the baseline-corrected total and free cortisol levels were negative because the observed total and free cortisol levels at baseline were higher than the total and free cortisol levels observed at this time point. Plasma total and free cortisol concentrations after administration of oral methylprednisolone were consistent with its known adrenal suppression (data not shown).[29]

The mean plasma free cortisol $AUEC_{24}$[BA] and $AUEC_{48}$[BA] were about 3-fold lower for RCI compared to synthetic $ACTH_{1\text{-}24}$ depot on day 1 (Table 5). On day 4, mean free cortisol $AUEC_{24}$[BA] and $AUEC_{48}$[BA] were about 4-fold and 5-fold lower, respectively, for RCI compared to synthetic $ACTH_{1\text{-}24}$ depot. Compared to day 1, E_{max24}[BA] was slightly higher on day 4 for RCI. Compared to synthetic $ACTH_{1\text{-}24}$ depot, E_{max24}[BA] was about 2-fold lower for RCI on days 1 and 4. Compared to synthetic $ACTH_{1\text{-}24}$ depot, median TE_{max24}[BA] occurred earlier for RCI on day 1 but was similar on day 4. Median TE_{max24}[BA] and TE_{max48}[BA] and mean E_{max24}[BA] and E_{max48}[BA] were the same as on day 1 and day 4 for RCI and synthetic $ACTH_{1\text{-}24}$ depot.

The mean serum total cortisol $AUEC_{24}$[BA] and $AUEC_{48}$[BA] values after a single dose (day 1) of RCI were about 2-fold and 3-fold lower, respectively, for total cortisol $AUEC_{24}$[BA] and $AUEC_{48}$[BA] than for values observed after administration of synthetic $ACTH_{1\text{-}24}$ depot (Table 5). After multiple doses (day 4), mean total cortisol $AUEC_{24}$[BA] and $AUEC_{48}$[BA] were about 3-fold lower for RCI than for synthetic $ACTH_{1\text{-}24}$ depot. Compared to day 1, E_{max24}[BA] was slightly higher on day 4 for both RCI and synthetic $ACTH_{1\text{-}24}$ depot. Median TE_{max24}[BA] was similar for day 1 and day 4 for both RCI and synthetic $ACTH_{1\text{-}24}$ depot but occurred earlier for RCI. Median TE_{max24}[BA] and TE_{max48}[BA] and mean E_{max24}[BA] and E_{max48}[BA] were the same as on day 1 and day 4 for RCI and synthetic $ACTH_{1\text{-}24}$ depot.

A comparison of total and free cortisol $AUEC_{24}$[BA] and $AUEC_{48}$[BA] using the least squares geometric mean ratio (percentage) of synthetic $ACTH_{1\text{-}24}$ depot to RCI is shown in Figure 7. Statistically significant differences ($P < 0.0001$) between synthetic $ACTH_{1\text{-}24}$ depot and RCI were observed on study day 1 and day 4 for both total and free $AUEC_{24}$[BA] (Figure 7A) and $AUEC_{48}$[BA] (Figure 7B), respectively.

Steroidogenic Exposure. The mean (SD) plasma free $AUEC_{24SG}$ of methylprednisolone on day 1 and day 4 was 572.0 ng • h/mL (184.0) and 492.0 ng • h/mL (136.0), respectively. The mean (SD) plasma total $AUEC_{24SG}$ of methylprednisolone on day 1 and

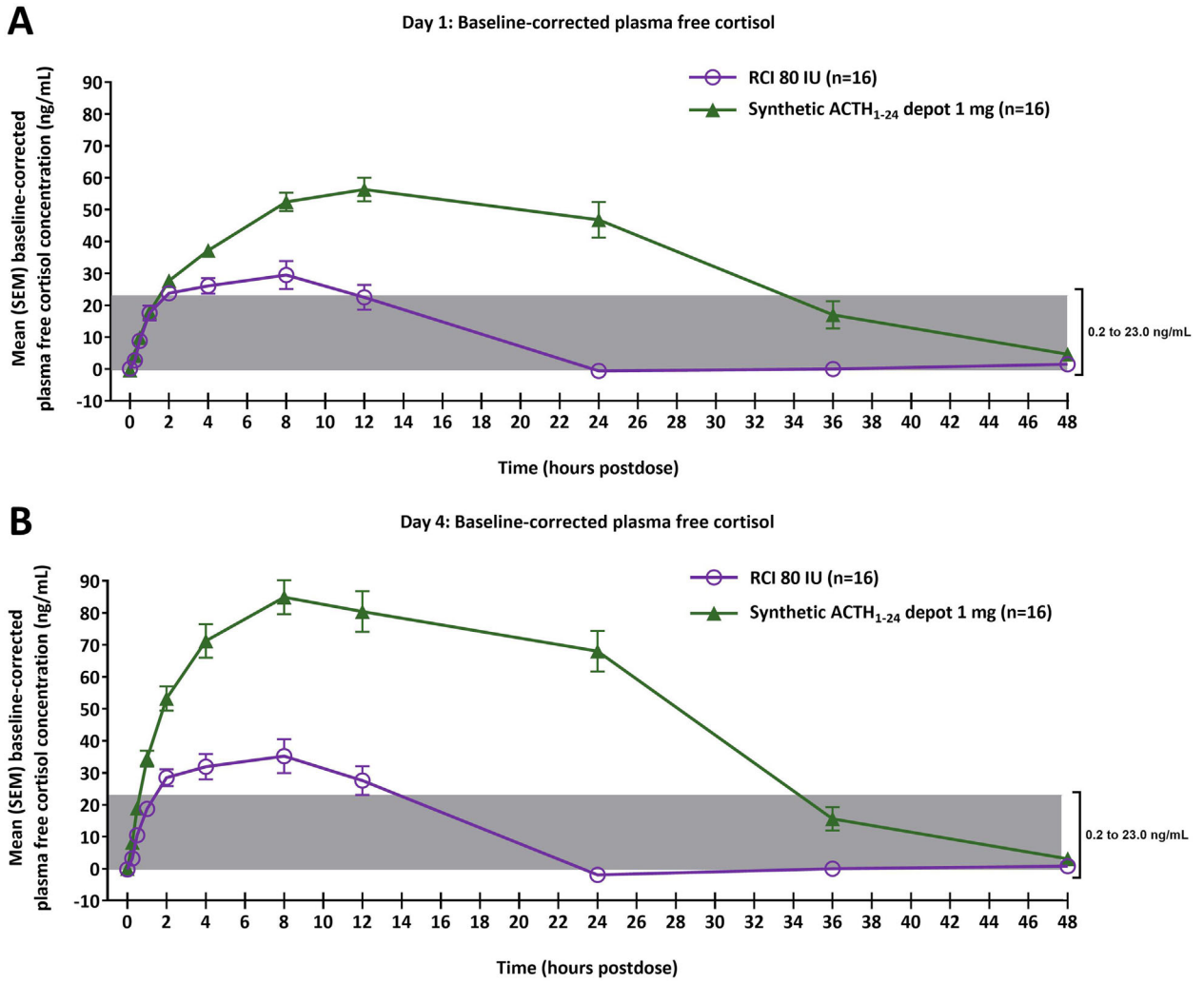

Figure 5. Mean (SEM) baseline-corrected[a] plasma free cortisol concentrations after administration of RCI and synthetic $ACTH_{1-24}$ depot on study day 1 (A) and day 4 (B). The range for baseline plasma free cortisol concentration observed for all study drugs is represented by the gray shaded area (0.2-23.0 ng/mL). [a]Baseline-corrected free cortisol concentrations were obtained by subtracting the time-matched baseline (day −1) free cortisol concentrations from the respective day 1 and day 4 free cortisol concentrations for each study drug. $ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; RCI, repository corticotropin injection; SEM, standard error of the mean.

day 4 was 6480.0 ng • h/mL (1770.0) and 5440.0 ng • h/mL (1330.0), respectively. E_{maxSG}, t_{maxSG}, and $AUEC_{24SG}$[BA] for total and free methylprednisolone are provided in Table S1.

Estimated Prednisone-Equivalent Doses. The estimated daily and weekly prednisone-equivalent doses of RCI 80 IU SC twice weekly were about 4-fold lower than that of synthetic $ACTH_{1-24}$ depot 1 mg SC twice weekly (Table 6).

Safety

All 48 subjects received at least 1 dose of RCI, synthetic $ACTH_{1-24}$ depot, or oral methylprednisolone. Most subjects (n = 39; 81%) reported at least 1 AE. Fewer subjects in the RCI group reported AEs than did subjects in either of the other 2 study drug groups (Table 7). The most common TEAEs in the RCI group were headache and injection site reaction; however, a lower incidence of injection site reactions was observed in the RCI group than in the synthetic $ACTH_{1-24}$ depot group. One subject in the synthetic $ACTH_{1-24}$ depot group experienced a TESAE of pulmonary embolism; no subjects in the RCI group or methylprednisolone group experienced any TESAEs.

No clinically significant changes from baseline in physical examination findings, vital signs, electrocardiogram findings, or clinical laboratory tests results, including serum chemistry, hematology, or urinalysis, were observed for subjects in any study drug group (data not shown).

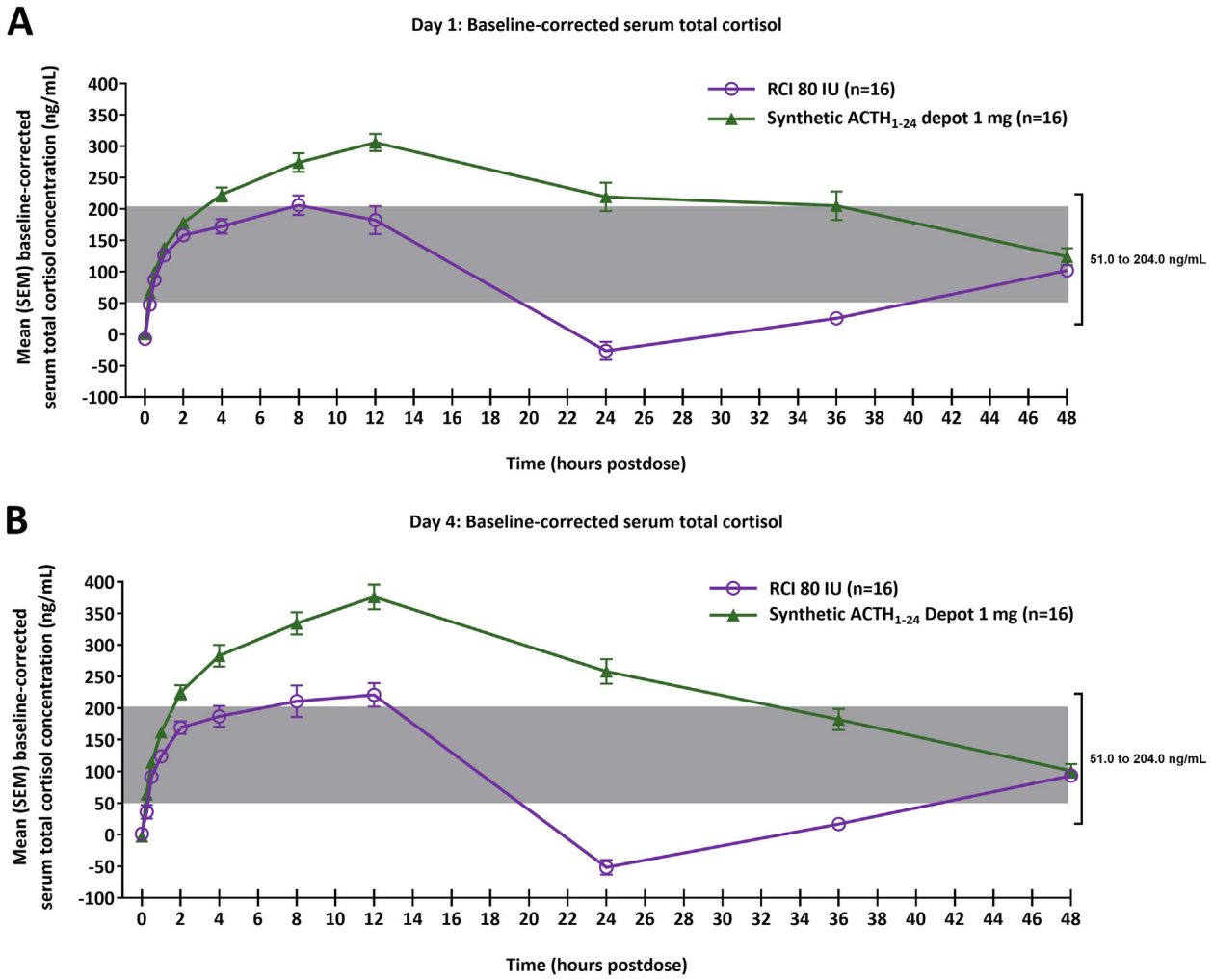

Figure 6. Mean (SEM) baseline-corrected[a] serum total cortisol concentrations after administration of RCI and synthetic $ACTH_{1-24}$ depot on study day 1 (A) and day 4 (B). The range for baseline serum total cortisol concentration observed for all study drugs is represented by the gray shaded area (51.0 to 204.0 ng/mL). [a]Baseline-corrected total cortisol concentrations were obtained by subtracting the time-matched baseline (day −1) total cortisol concentrations from the respective day 1 and day 4 total cortisol concentrations for each study drug. $ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; RCI, repository corticotropin injection; SEM, standard error of the mean.

Discussion

Since therapeutic use of ACTH analog formulations became widespread in the 1950s and 1960s, studies have demonstrated variable cortisol responses after administration of different ACTH products.[24,25,33,34] This phase 1, single-center, open-label, randomized parallel group study is the first to report a direct comparison of the cortisol responses of RCI and synthetic $ACTH_{1-24}$ depot.

Administration of doses of RCI and synthetic $ACTH_{1-24}$ depot used to treat nephrotic syndrome resulted in substantially different levels of endogenous cortisol production. After twice-weekly SC administration of each drug, RCI induced >2-fold lower mean peak baseline-corrected plasma free cortisol concentrations than synthetic $ACTH_{1-24}$ depot. Because endogenous cortisol production is mediated by the activation of MC2R on adrenal cortical cells,[35] the lower cortisol response observed for RCI is consistent with preclinical findings that suggest that it has a lower functional activity at MC2R than does synthetic $ACTH_{1-24}$ depot.[23] Consequently, RCI may exhibit fewer steroidal effects than synthetic $ACTH_{1-24}$ depot, which warrants further investigation.

RCI also induced a 5-fold lower plasma free cortisol exposure than synthetic $ACTH_{1-24}$ depot after 2 doses. Further, the ratio of total and free cortisol exposure for synthetic $ACTH_{1-24}$ depot to RCI showed significantly lower total and free cortisol exposure after administration of RCI compared to synthetic $ACTH_{1-24}$

Table 5. Mean (SD)[a] Plasma Free and Serum Total Cortisol Pharmacodynamic Parameters After Administration of RCI and Synthetic $ACTH_{1-24}$ Depot

	RCI 80 IU SC Twice Weekly (N = 16)		Synthetic $ACTH_{1-24}$ Depot 1 mg SC Twice Weekly (N = 16)	
	Day 1	Day 4	Day 1	Day 4
Free cortisol[b,c]	n = 14	n = 14	n = 13	n = 13
E_{max24}, ng/mL	36.0 (10.7)	40.8 (17.6)	61.8 (17.1)	89.8 (24.8)
E_{max24}[BA], ng/mL	35.8 (10.7)	40.6 (17.7)	61.5 (17.0)	89.5 (24.9)
TE_{max24}, h	8.0 (2.0, 12.0)	8.0 (2.0, 8.0)	12.0 (8.0, 23.9)	8.0 (8.0, 23.8)
TE_{max24}[BA], h	8.0 (2.0, 12.0)	8.0 (2.0, 8.0)	12.0 (8.0, 23.6)	8.0 (8.0, 23.8)
$AUEC_{24}$, ng • h/mL	466 (214)	501 (261)	1150 (312)	1740 (522)
$AUEC_{24}$[BA], h • ng/mL	361 (164)	395 (187)	1140 (315)	1730 (525)
$AUEC_{48}$, ng • h/mL	566 (211)	718.0 (414)	1170 (656)	2380 (797)
$AUEC_{48}$[BA], ng • h/mL	624 (359)	490 (249)	1680 (665)	2340 (795)
Total cortisol[c]	n = 16	n = 16	n = 13	n = 13
E_{max24}, ng/mL	268.0 (42.4)	284.0 (65.1)	358.0 (63.4)	416.0 (74.7)
E_{max24}[BA], ng/mL	222.0 (47.0)	240.0 (72.8)	318.0 (61.0)	380.0 (84.9)
TE_{max24}, h	8.0 (1.0, 12.0)	8.0 (2.0, 12.0)	12.0 (8.0, 23.6)	12.0 (8.0, 23.8)
TE_{max24}[BA], h	8.0 (1.0, 12.1)	8.0 (2.0, 12.0)	12.0 (8.0, 23.6)	12.0 (8.0, 23.8)
$AUEC_{24}$, ng • h/mL	4440 (1110)	4680 (1180)	7520 (1160)	8760 (1400)
$AUEC_{24}$[BA], ng • h/mL	2480 (964)	2410 (887)	6010 (1310)	7250 (1570)
$AUEC_{48}$, ng • h/mL	5870 (1210)	5790 (1260)	12 800 (2920)	13 700 (2560)
$AUEC_{48}$[BA], ng • h/mL	3480 (1470)	3550 (1730)	9450 (3270)	10 400 (2720)

$ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; $AUEC_{24}$, area under the effect curve for the concentration-time profile from time 0 to 24 hours; $AUEC_{48}$, area under the effect curve for the concentration-time profile from time 0 to 48 hours; BA, baseline-corrected; E_{max24}, maximum observed effect at 24 hours; RCI, repository corticotropin injection; SC, subcutaneously; SD, standard deviation; TE_{max24}, time to maximum observed effect at 24 hours.

[a] TE_{max24} and TE_{max24}[BA] are presented as median (minimum, maximum).

[b] In the RCI and synthetic $ACTH_{1-24}$ groups, 2 subjects and 3 subjects, respectively, did not have at least 4 consecutive quantifiable plasma concentrations of free cortisol on both day −1 and day 1 and therefore were not included in these analyses.

[c] Results for E_{max48} and TE_{max48} are not reported, as they are the same as E_{max24} and TE_{max24}, respectively.

Table 6. Estimated Prednisone-Equivalent Doses of RCI and Synthetic $ACTH_{1-24}$ Depot

	Weekly Prednisone Dose (mg)	Daily Prednisone Dose (mg)
RCI 80 IU SC twice weekly (160 IU per week)	67	10
Synthetic $ACTH_{1-24}$ depot 1 mg SC twice weekly (2 mg per week)	291	42

$ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; RCI, repository corticotropin injection; SC, subcutaneous.

depot. Comparisons between total and free cortisol exposure for RCI and synthetic $ACTH_{1-24}$ depot with total and free steroidogenic exposure of methylprednisolone would not be appropriate due to differences in dosing regimens. In this study, oral methylprednisolone was given once daily on study days 1 through 6, while RCI and synthetic $ACTH_{1-24}$ depot were given as SC doses on study day 1 and day 4. However, these dosage regimens were consistent with clinically relevant maintenance doses used for each study drug when treating nephrotic syndrome.[8,12,28]

Results from this study estimated a low daily prednisone-equivalent dose for RCI, with 80 IU SC twice weeky corresponding to 10 mg/d of prednisone. In contrast, synthetic $ACTH_{1-24}$ 1 mg SC twice weekly was found to be comparable to estimated doses of prednisone that were about 4-fold higher than for RCI. A previous model-based simulation study found the prednisone-equivalent dose of RCI to be about 7-fold lower than that of synthetic $ACTH_{1-24}$ depot at the same clinically relevant doses.[27] However, this simulation used data from 2 separate PK/PD studies and did not directly measure plasma free cortisol exposure after administration of synthetic $ACTH_{1-24}$ depot 1 mg SC twice weekly. Thus, the current findings reflect estimates of the actual in vivo steroidal exposure of these clinically relevant dosing regimens. Nevertheless, both studies found RCI to have a substantially lower prednisone-equivalent dose than clinically relevant doses of synthetic $ACTH_{1-24}$ depot. Despite having a low estimated daily prednisone-equivalent dose, RCI has previously

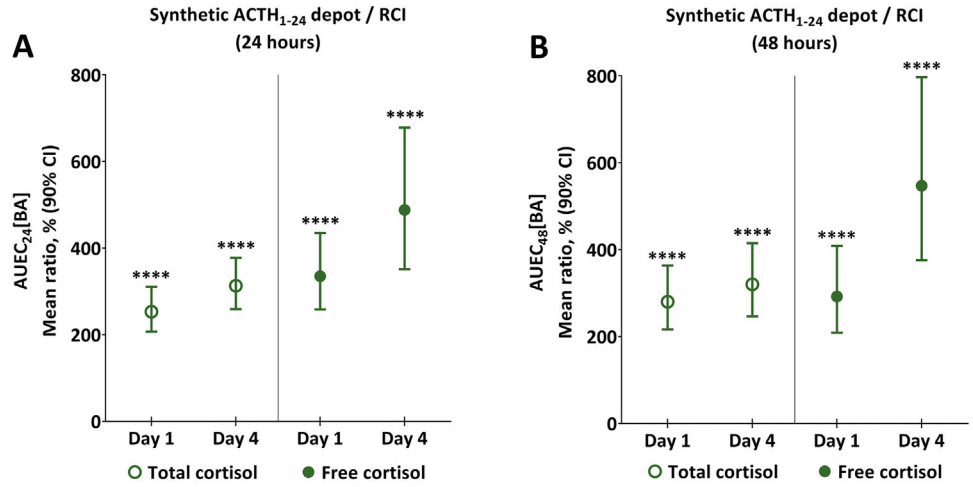

Figure 7. Comparison of serum total and plasma free cortisol $AUEC_{24}$[BA] (A) and $AUEC_{48}$[BA] (B) using the LS geometric mean ratio (percentage) of synthetic $ACTH_{1-24}$ depot to RCI. ****$P < 0.0001$ for the LS geometric means ratio (percentage) of synthetic $ACTH_{1-24}$ depot to RCI for each day using ANOVA models, with study drug as a fixed effect and subject as a random effect. $ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; ANOVA, analysis of variance; $AUEC_{24}$[BA], baseline-corrected area under the effect curve for the concentration-time profile from time 0 to 24 hours; $AUEC_{48}$[BA], baseline-corrected area under the effect curve for the concentration-time profile from time 0 to 48 hours; CI, confidence interval; LS, least squares; RCI, repository corticotropin injection.

Table 7. Adverse Events

	RCI 80 IU SC twice weekly n = 16	Synthetic $ACTH_{1-24}$ Depot 1 mg SC twice weekly n = 16	Methylprednisolone Tablets 32 mg Orally Daily n = 16	All Subjects N = 48
AEs, n	22	55	17	94
Subjects with any TEAE, n (%)	12 (75.0)	15 (93.8)	10 (62.5)	37 (77.1)
Most common TEAEs (≥4% in any study drug group), n (%)				
Contusion	1 (6.3)	2 (12.5)	1 (6.3)	4 (8.3)
Dysuria	0	2 (12.5)	0	2 (4.2)
Headache	3 (18.8)	1 (6.3)	2 (12.5)	6 (12.5)
Heart palpitations	1 (6.3)	4 (25.0)	2 (12.5)	7 (14.6)
Injection site reaction	3 (18.8)	12 (75.0)	0	15 (31.0)
Insomnia	0	2 (12.5)	0	2 (4.2)
Somnolence	2 (12.5)	0	0	2 (4.2)
Any TESAE, n (%)	0	1 (6.3)	0	1 (2.1)
Pulmonary embolism	0	1 (6.3)	0	1 (2.1)

$ACTH_{1-24}$, the first 24 amino acids of adrenocorticotropic hormone; AE, adverse event; RCI, repository corticotropin injection; SC, subcutaneous; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

demonstrated clinical efficacy in patients with inflammatory conditions that have shown a poor clinical response to corticosteroids.[8–18] This further supports a therapeutic effect of RCI that is independent of cortisol production and suggests that RCI may be an efficacious alternative for patients who have become resistant to the effects of corticosteroids or are unable to tolerate their side effects.

Interestingly, lower endogenous cortisol production after administration of RCI was observed despite having a slightly higher mean elimination half-life compared to synthetic $ACTH_{1-24}$ depot after multiple doses. Synthetic $ACTH_{1-24}$ depot achieved rapid peak concentrations similar to RCI and rapidly eliminated with no quantifiable plasma concentrations observed after 8 hours postdose for 88% of the subjects. Further, mean plasma N25D porcine $ACTH_{1-39}$ (the PK marker for RCI) concentrations were higher than mean plasma $ACTH_{1-24}$ concentrations (Figures 2 and 3, respectively), yet RCI induced 2-fold less cortisol than

synthetic $ACTH_{1-24}$ depot after multiple doses (Figure 5B). The lower endogenous cortisol response of RCI despite its having higher plasma concentrations could be explained by its complex mixture of peptides and the heterodimeric nature of MCRs.[36] Further research is needed to elucidate the mechanisms of RCI.

Safety results were consistent with the known safety profile for RCI. Fewer injection site reactions were observed in the RCI group than in the synthetic $ACTH_{1-24}$ depot group (18.8% and 75.0%, respectively). No TESAEs were reported in the RCI group; however, 1 subject receiving synthetic $ACTH_{1-24}$ depot experienced a TESAE of pulmonary embolism.

This study has several limitations. As an open-label study, subjects and investigators were aware of study drug assignments. The study was conducted in a small sample of healthy subjects; thus, the clinical relevance of these findings should be investigated in a larger sample of patients who have inflammatory conditions.

RCI is a complex mixture of modified porcine ACTH and other related peptide analogs. At clinically relevant maintenance doses used for the treatment of nephrotic syndrome, RCI induced less endogenous cortisol production and had lower cortisol exposure and lower steroidogenic exposure than synthetic $ACTH_{1-24}$ depot after twice-weekly administration. These results are supported by the clinical efficacy of RCI in the treatment of inflammatory disorders that have previously demonstrated an inadequate response to corticosteroids.[8–18] The different PD properties observed for RCI and synthetic $ACTH_{1-24}$ depot in this study suggest that these products in the ACTH class are not interchangeable.

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Conflicts of Interest

All authors were employees of Mallinckrodt Pharmaceuticals at the time of study completion.

Author Contributions

All authors contributed to the conception or design of the work, acquisition, analysis, or interpretation of data, drafting the work or revising it critically for important intellectual content, and final approval of the version to be published.

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Data Sharing

The data sets generated and analyzed for this article are not publicly available. Requests for additional information should be made to the corresponding author.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.