CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-028

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-028	Submission Date: 02-03-2006
Brand Name	Cosyntropin
Generic Name	Cosyntropin for injection
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCP Division	Division of Clinical Pharmacology 2
ORM division	Division of Metabolic and Endocrine Products
Sponsor	Sandoz Canada, Inc.
Relevant IND(s)	69,720
Submission Type; Code	Original
Formulation; Strength(s)	0.25 mg solution
Dosing regimen	Diagnostic agent, 0.25 mg IV
Indication	Screening of adrenocortical insufficiency

Table of Contents

1. EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

From the Clinical Pharmacology standpoint, the application is acceptable. This recommendation and the labeling comments should be conveyed to the sponsor as appropriate.

1.2 Labeling comments:

From the bioequivalence study, the peak time for cortisol response has been indicated between 2.25 to 2.5 hours, which is much longer than that described in the ordinal package insert as [redacted] minutes. A figure showing the cortisol response may be included in the labeling. This information should be updated. Since the pH is [redacted] for Cosyntropin, which can be painful if the drug is administered via intramuscular injection. Therefore, it should be clearly described in the label that Cosyntropin should not be given intramuscularly due to [redacted]

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1.3 Phase IV

None

1.4. Summary of Clinical Pharmacology Findings

This is a 505 (b) (2) application to seek marketing of Cosyntropin, a synthetic partial sequence (α 1-24 amino acids) of ACTH. The reference drug product is Amphastar's synthetic cosyntropin, Cortrosyn, which was approved in 1970 under NDA16-750. Based on an agreement with the Agency, there is no requirement for the pharmacokinetic data to demonstrate bioequivalence because of the route of intravenous administration.

Cosyntropin exhibits the full corticosteroidogenic activity of natural ACTH. It has been established that 0.25 mg of cosyntropin will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. Cosyntropin injection is intended for use as a diagnostic agent in the screening of patients with adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it has been utilized to perform a 30-minute test of adrenal function in most cases.

To support this 505 (b) (2) application, the sponsor conducted a single center, randomized, single-dose, open-label, 2-way crossover bioequivalence study. The sponsor compared the plasma cortisol concentration response, a pharmacodynamic marker, of a test drug product cosyntropin versus Cortrosyn, a reference cosyntropin, under fasting conditions. A single dose of cosyntropin as a 1 mL x 0.25 mg/mL injection was administered intravenously in each study period. The treatment phases were separated by a washout period of 5 days. The sponsor used both baseline corrected and uncorrected data for BE analysis. The results using baseline corrected data showed that $AUC_{0\text{-}inf}$ and C_{max} passed the BE acceptance criterion. In conclusion, the cortisol response was comparable between the test cosyntropin (Treatment A) and the reference Cortrosyn (Treatment B) following 0.25 mg intravenous dose.

Note: An Optional Intra-Division Level CP Briefing was held on December 1. Chandra Sahajwalla, Suresh Doddapaneni, Hae-Young Ahn, Bill Lubas and this reviewer were present.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulations of the drug product?

Cosyntropin Injection is a 1 mL sterile solution in vials containing 0.25 mg of Cosyntropin, 0.82 mg sodium acetate trihydrate, 6.4 mg sodium chloride, 10 mg mannitol, 1 mg glacial acetic acid, and water for injection, USP. Administration is by intravenous injection. Cosyntropin is α 1-24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The sequence of amino acids in the 1-24 compound is as follows:

Ser - Tyr - Ser - Met - Glu - His - Phe - Arg - Trp - Gly - Lys
1 2 3 4 5 6 7 8 9 10 11
Pro - Val - Gly - Lys - Lys - Arg - Arg - Pro - Val - Lys - Val
12 13 14 15 16 17 18 19 20 21 22
Tyr - Pro
23 24

2.1.2 What is the mechanism of action, therapeutic indication and dosage recommendations for Cosyntropin?

Mechanism of Action:

Cosyntropin exhibits the full corticosteroidogenic activity of natural ACTH. Various published studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1 - 20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residues. For example, the decrement from 20 to 19 results in a 70% loss of potency.

The pharmacologic profile of cosyntropin is similar to that of purified natural ACTH. It has been established that 0.25 mg of cosyntropin will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of cosyntropin injection will produce maximal secretion of 17-OH corticosteroids, 17-keto steroids and/or 17 -ketogenic steroids.

The extra-adrenal effects which natural ACTH and cosyntropin injection have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.

Animal, human and synthetic ACTH (1-39) which all contain 39 amino acids exhibit similar immunologic activity. This activity resides in the C-terminal portion of the molecule and the 22-39 amino acid residues exhibit the greatest degree of antigenicity. In contrast, synthetic poly-peptides containing 1-19 or fewer amino acids have no detectable immunologic activity. Those containing 1-26, 1-24 or 1-23 amino acids have very little immunologic activity although full biologic activity. This property of cosyntropin injection assumes added importance in view of antigenicity of natural ACTH.

Proposed Indications

Cosyntropin injection is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it may be utilized to perform a 30-minute test of adrenal function.

Proposed Dosage Recommendation

Cosyntropin injection may be administered as a direct intravenous injection when used as a rapid screening test of adrenal function. It may also be given as an intravenous infusion over a 4 to 8 hour period to provide a greater stimulus to the adrenal glands. Doses of cosyntropin injection 0.25 to 0.75 mg have been used in clinical studies and a maximal response noted with the smallest dose.

2.2 GENERAL CLINICAL PHARMACOLOGY

Based on an agreement with the Agency during a Pre-NDA meeting dated September 22, 2004, there is no requirement for the pharmacokinetic data to demonstrate bioequivalence because of the route of intravenous administration.

2.2.1 What are the pharmacodynamic response profiles of Cosyntropin following a single bolus intravenous administration in healthy subjects?

In a single center, randomized, single-dose, open-label, 2-way crossover bioequivalence study, the sponsor compared the plasma cortisol concentration response, a pharmacodynamic marker, of a test drug product cosyntropin versus Cortrosyn, a reference cosyntropin, under fasting conditions. A single dose of cosyntropin as a 1 mL x 0.25 mg/mL injection was administered intravenously in each study period. The blood samples were collected 1, 0.5, and 0.25 hours pre-dose and 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, and 6.00 hours post-dose in each period. A total of 24 subjects were recruited and 22 subjects completed the study. The treatment phases were separated by washout period of 5 days. The summary of pharmacodynamic response is presented in Figure 1 and Table 1.

Figure 1. The time-concentration profiles of Cosyntropin (test drug) and Cortrosyn (LDP) after intravenous administration in healthy human subjects (baseline corrected)

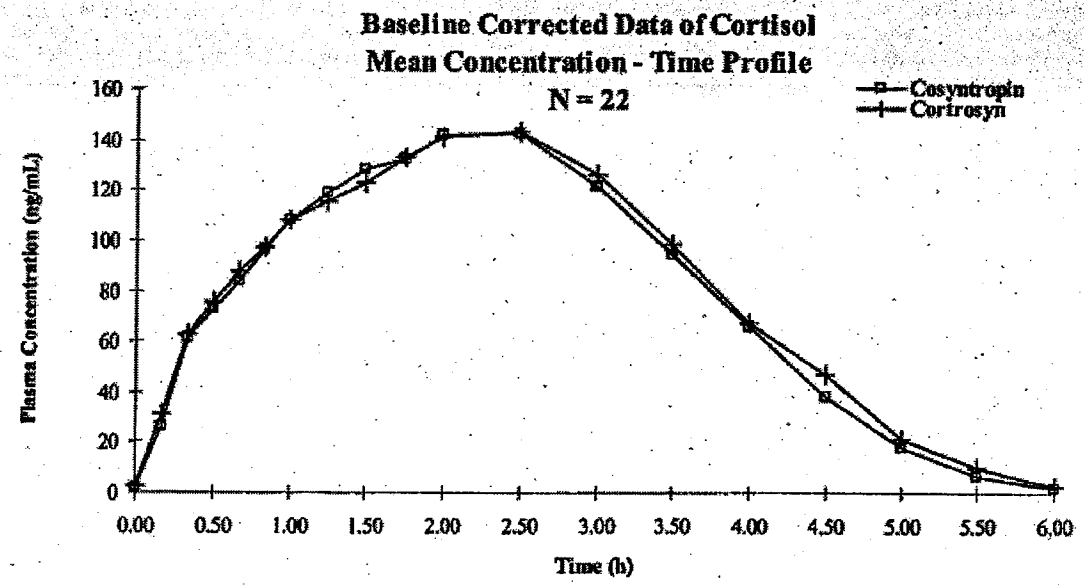

Table 1. Summary of pharmacodynamic parameters with baseline corrected data of cortisol.

Parameters		Test (Cosyntropin (A)) Mean	±	SD	CV (%)	Reference (Cortrosyn (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	470.39	±	166.76	35.45	481.19	±	222.63	46.27
AUC_{0-inf}	(ng·h/mL)	480.69	±	166.35	34.61	504.30	±	214.33	42.50
$AUC_{t/inf}$	(%)	97.66	±	2.28	2.34	93.25	±	10.24	10.98
C_{max}	(ng/mL)	153.02	±	38.90	25.42	152.50	±	50.88	33.36
T_{max}	(h)	2.31	±	0.55	23.63	2.27	±	0.39	17.28
T_{max}*	(h)	2.25	±	0.51	-	2.50	±	0.50	-
K_{el}	(h^{-1})	1.7561	±	0.8628	49.13	1.1732	±	0.3860	32.90
$T_{½ el}$	(h)	0.46	±	0.16	34.25	0.69	±	0.40	57.93

The results of bioequivalence analysis are presented in Table 2. Obviously, the The Cmax and AUC 0-inf remain within 90% CI. However, the 90% CI for AUC0-t is a little off the upper boundary limit as 126.47%.

Table 2. Bioequivalence analysis [Cosyntropin (A, test) vs. Cortrosyn (B, reference)]

	AUC_{0-inf}	C_{max}
Ratio	100.99%	104.15%
90% Geometric confidence Interval	87.61 – 116.41	92.54 – 117.23
Intra-subject CV	27.73%	22.94%

It is noted that Subject #5 did not respond to the reference drug product at 30 min and before. Therefore, the cortisol levels for the baseline corrected data for the 30 min time point after administration was negative and was then set to zero for Subject #5. The sponsor conducted additional bioequivalence analysis excluding Subject #5 (N = 21). As a consequence, the 90% confidence intervals are within 80 -125% criteria.

Cosyntropin is intended for use as a diagnostic agent for adrenocortical insufficiency. The diagnostic test consists of measuring plasma cortisol levels in response to a cosyntropin injection. Based on the labeling of reference drug product, plasma cortisol concentrations usually peak between 30 and 60 minutes after an injection of cosyntropin and the 30 and/ or 60 minute plasma cortisol concentrations should be used as the single criterion for this diagnostic test. Therefore, the sponsor collected two time points for cortisol concentrations at 30 min and 60 min. The cortisol data is summarized in Table 3.

Table 3. Summary of analysis for cosyntropin response at 30 and 60 minutes (baseline corrected data, N=22)

Parameter	Test [Cosyntropin A)]		Reference [Cortrosyn (B)]	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
$C_{30\ min}$ (ng/mL)*	74.18±20.77	28.00	79.32±32.65	41.16
$C_{60\ min}$ (ng/mL)	107.82±30.17	27.98	107.98±40.03	37.07

- For this parameter, N=21.

The sponsor also performed a bioequivalence analysis for the ratios of these two time point estimates. The results have showed that they are remained inside of BE criteria (Table 4).

Table 4. Cosyntropin (A) vs Cortrosyn (B)

Parameter	C_{30} min*	C_{60} min
Ratio	100.44%	105.93%
90% Geometric CI	83.67 – 120.58	92.68 – 121.08
Intra-subject CV	34.88%	26.01%

- For this parameter, N=21.

Reviewer's comments:

It is indicated in the package insert of the reference drug product (Cortrosyn) that the plasma cortisol levels usually peak about 45 to 60 minutes after an injection of cosyntropin and the diagnostic test is based on cortisol response at 30 or 60 minutes. Based on this PD bioequivalence study, T_{max} for cortisol response is between 2.25 and 2.5 hours for the test drug product and the reference drug product, respectively. However, the current diagnostic criteria are based on 30 or 60 minutes. The package insert should modify the description of peaked response.

It is strange that Subject #5 did not respond to the reference drug product until after 30 minutes (see Figure below). The sponsor did not describe any possible causes.

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Although there is no regulatory policy on pharmacodynamic parameters for bioequivalence acceptance criteria, the sponsor's additional analysis for data excluding Subject #5 demonstrated the 90% confidence interval is within BE acceptance criteria, which provides additional support to their claim of bioequivalence between the two products. This reviewer agrees that the cortisol response is comparable between the test cosyntropin (Treatment A) and the reference Cortrosyn (Treatment B) following 0.25 mg intravenous dose.

2.3 ANALYTICAL

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A high performance liquid chromatographic method using spectrometry detection (LC MS MS) was used for the determination of cortisol in human EDTA plasma. The method was validated by the bioanalytical division of

During this validation, the term unstripped refers to regular human EDTA plasma and the term charcoal stripped refers to plasma which was treated with activated charcoal to remove endogenous levels of cortisol prior to use. Validation parameters were evaluated with both matrices, unless mentioned otherwise, to verify that a standard curve made in stripped plasma would permit accurate measurement of cortisol in unstripped samples.

Cortisol is extracted from an aliquot of both charcoal stripped and unstripped human EDTA plasma using an

Quantitation is by peak area ratio method. A weighted ($1/C^2$) linear regression is performed to determine the concentration of the analyte. All regressions and figures presented in this validation report were generated by MDS Sciex Analyst software version 1.4. A summary of the validation results is presented in Table 2.

Table 6. Assay validation results for plasma cortisol samples

Calibration curve range:	
Quantitation limit	2.01 ng/mL
Between-run CV of LLOQ (Precision)	6.93 %
Between-run % nominal of LLOQ (Accuracy)	100.50 %
Between-Run Accuracy (Charcoal Stripped)	
Between-Run Precision (Charcoal Stripped)	CV=

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Between-Run Accuracy (Unstripped)	[redacted]
Between-Run Precision (Unstripped)	CV= [redacted]
Within-Run Accuracy (Charcoal Stripped)	[redacted]
Within-Run Precision (Charcoal Stripped)	CV= [redacted]
Within-Run Accuracy (Unstripped)	[redacted]
Within-Run Precision (Unstripped)	CV= [redacted]

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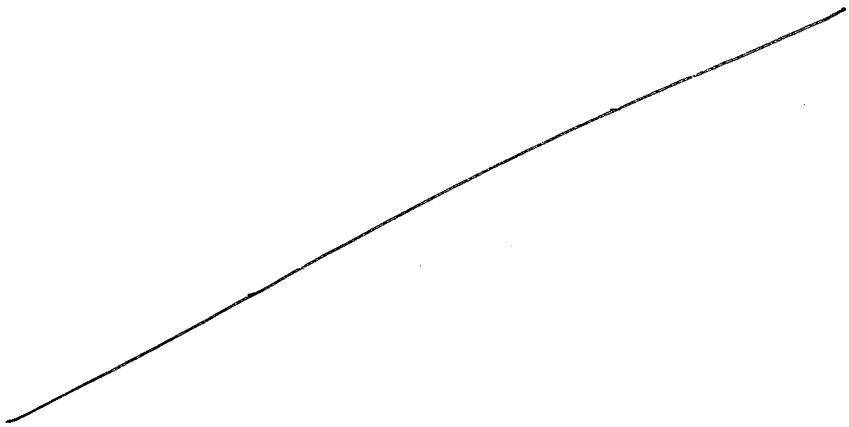
3 DETAILED LABELING RECOMMENDATIONS

(~~Strikeout text~~ should be removed from labeling; underlined text should be added to labeling)

DOSAGE AND ADMINISTRATION



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b(5)

APPEARS THIS WAY
ON ORIGINAL

4 APPENDICES

4.1 NDA FILING MEMO

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA Number	**22-028**	**Brand Name**	**N/A**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Cosyntropin injection**
Medical Division	**HFD-510**	**Drug Class**	**peptide**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Diagnosis of adrenal insufficiency**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**solution**
		Strength	**0.25 mg/mL**
Date of Submission	**02-06-2006**	**Route of Administration**	**SC**
Estimated Due Date of OCPB Review	**10-15-2006**	**Sponsor**	**Sandoz**
PDUFA Due Date	**12-06-2006**	**Priority Classification**	**S1**
Division Due Date	**11-01-2006**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**Yes**	
Comments sent to firm?	**No**	

Submission:

Sandoz Canada Inc. is seeking approval of Cosyntropin injection 0.25 mg/mL, aqueous formulation, based on the listed drug product, Amphastar's Cortrosyn™ for Injection 0.25 mg (lyophilized powder), which is identified in the Orange Book, "Approved Drug Products with Therapeutic Equivalence Evaluations" (NDA 16-750, CORTROSYN™).

CORTROSYN™ contains cosyntropin as the active ingredient, and is a sterile lyophilized powder for injection solely for administration by intramuscular and intravenous injection.

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Sandoz 505(b)(2) NDA product, Cosyntropin Injection 0.25 mg/mL, has the same active ingredient in the same concentration and strength as the RLD with the exception of ingredients added to [redacted] Sandoz Cosyntropin Injection 0.25mg/mL is formulated as a sterile aqueous solution [redacted]

Product	Route of Administration	Dosage	Form
RLD Cortrosyn™ for injection	Intramuscular Intravenous	0.25 mg	0.25 mg lyophilized powder to be reconstituted with 1 mL 0.9 % NaCL
Sandoz Cosyntropin Injection	Intravenous	0.25 mg	0.25 mg/mL aqueous solution

Sandoz requests a therapeutically equivalent rating and TE code to the RLD (CORTROSYN™) upon approval of this application.

In order to demonstrate the bioequivalence between Sandoz Cosyntropin and the reference drug Cortrosin™, the sponsor conducted a BE study in 24 healthy subjects using PD parameters for cortisol as the primary markers. The sponsor used baseline corrected analysis as the primary method and baseline uncorrected analysis as a supportive method. The pharmacokinetic parameters were not analyzed.

The assay validation, QC study and PD datasets are submitted for review.

4.2 INDIVIDUAL STUDY REVIEW

SYNOPSIS (Study Code: 50525)

Study title:
Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (Reference) Following a 0.25 mg Intravenous Dose In Healthy Subjects

Date of Final Report: 2005-12-12

Investigators:

[redacted]

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Study Center:

[redacted]

Dates of the Clinical Portion: 2005-10-12 to 2005-10-17

Clinical Phase: I (Bioequivalence)

Objective:
The objective of this study was to compare the plasma cortisol concentration response of Sandoz Canada Inc., Canada, cosyntropin and Amphastar (Cortrosyn), cosyntropin, administered as a 1 mL x 0.25 mg/mL injection, under fasting conditions.

Study Design:
This was a single center, randomized, single-dose, open-label, 2-way crossover bioequivalence study to compare the plasma cortisol concentration response of a test cosyntropin versus Cortrosyn, a reference cosyntropin, under fasting conditions. Subjects were confined to the [redacted] from at least 10 hours prior to drug administration, until approximately 8 hours post-dose, in each period. The treatment phases were separated by washout period of 5 days. b(4)

Subjects:
- Enrolled and randomized: 24 (13 males and II females)
- Drop-out: 1
- Withdrawal: 1
-Completed: 22
- Data set for safety analysis: 24
- Data set for statistical analysis: 22

Diagnosis and Main Criteria for Inclusion:
Subjects had to be healthy, adult non-smokers, 18 years and older; body mass indices 2: 19.0 and.: 30.0 kg/m2. All subjects had to meet the inclusion and exclusion criteria described in the protocol and were judged eligible for enrollment in this study, based on medical and medication histories, demographic data (including sex, age, race, body weight (kg), height (cm) and BMI (kg/m2)), vital signs measurements, 12-lead ECG, physical examination, a urine drug screen, urine pregnancy test (for all females), and clinical laboratory tests (hematology, biochemistry (including morning plasma cortisol), urinalysis, HIV, hepatitis C (HCV) antibodies and hepatitis B surface antigens.

Treatment:	Test (A)	Reference (B)
Name:	cosyntropin	cosyn tropin (Cortosyn II)
Unit dose:	0.25 mg/mL	0.25 mg/mL
Regimen:	single dose of 1 mL x 0.25mg/mL injection per subject in accordance with the randomization scheme	
Lot No.:	1200503-F	XC038E5
Manufacturer:	Sandoz Canada Inc., Canada;	[redacted]

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Duration of Treatment: A single dose of cosyntropin as a 1 mL x 0.25 mg/mL injection was administered in each study period. The treatment phases were separated by a washout period of 5 days.

Blood Sampling Points: Blood samples were collected 1, 0.5, and 0.25 hours prior to drug administration and 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00,4.50, 5.00, 5.50, and 6.00 hours post-dose in each period.

Analytical Method: Analyte: cortisol Plasma samples were used for analysis.

- Method: LC MS MS
-Quantitation limit: 2.01 ng/mL
- Sample analysis calibration curve range: b(4)
-Between-run CV of LLOQ (Precision):
-Between-run % nominal of LLOQ (Accuracy):

Criteria for Evaluation:
Pharmacodynamics:
AUC0-t, AUC0-inf, Cmax, AUCt/inf, Tmax, T1/2 el and Kel

Safety:
Adverse events, vitals signs measurements, and standard laboratory evaluations.

Statistical Methods:
Pharmacodynamics:
- Parametric ANOVA on AUC0-t, AUC0-inf, Cmax, Tmax, T1/2el; geometric confidence intervals for AUC0-t, AUC0-inf and Cmax;
- Covariates in the ANOVA model: sequence, subject within sequence, period and treatment;
- Ln-transformed parameters: AUC0-t, AUC0-inf and Cmax, estimated only for the baseline corrected data of cortisol.

Criteria for Bioequivalence:
- For the baseline corrected data of cortisol, the 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf, and Cmax should be within 80.00% to l25.00%. - The results without baseline correction were provided as supportive data only.

Results:
Pharmacodynamics:
SUMMRY OF RESULTS of BASELINE CORRCTED DATA OF CORTISOL
Pharmacodynamic Parameters (N=22)

Pharmacodynamic Parameters

Parameters		Test (Cosyntropin (A)) Mean	±	SD	CV (%)	Reference (Cortrosyn (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	470.39	±	166.76	35.45	481.19	±	222.63	46.27
AUC_{0-inf}	(ng·h/mL)	480.69	±	166.35	34.61	504.30	±	214.33	42.50
$AUC_{t/inf}$	(%)	97.66	±	2.28	2.34	93.25	±	10.24	10.98
C_{max}	(ng/mL)	153.02	±	38.90	25.42	152.50	±	50.88	33.36
T_{max}	(h)	2.31	±	0.55	23.63	2.27	±	0.39	17.28
T_{max}*	(h)	2.25	±	0.51	-	2.50	±	0.50	-
K_{el}	(h^{-1})	1.7561	±	0.8628	49.13	1.1732	±	0.3860	32.90
$T_{½ el}$	(h)	0.46	±	0.16	34.25	0.69	±	0.40	57.93

* Medians and interquartile ranges are presented.

Cosyntropin (A) vs Cortrosyn (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	106.96%	100.99%	104.15%
90 % Geometric C.I.[2]	90.45 % to 126.47 %	87.61 % to 116.41 %	92.54 % to 117.23 %
Intra-Subject CV	32.94 %	27.73 %	22.94 %

N = 21, Analysis Excluding Subject No. 05

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.54%	98.91%	103.05%
90 % Geometric C.I.[2]	87.89 % to 124.34 %	85.43 % to 114.52 %	91.03 % to 116.65 %
Intra-Subject CV	33.02 %	27.69 %	23.31 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Cosyntropin (A)} - \text{Cortrosyn (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data

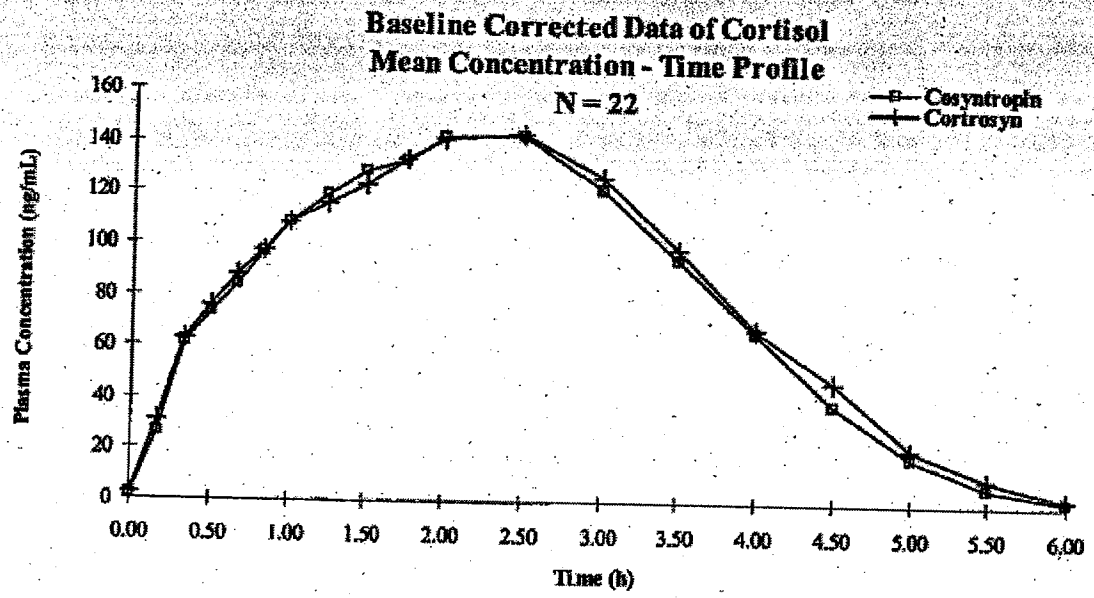
SUMMARY OF RESULTS OF ADDITIONAL ANALYSES BASELINE CORRECTED DATA OF CORTISOL (N=22)

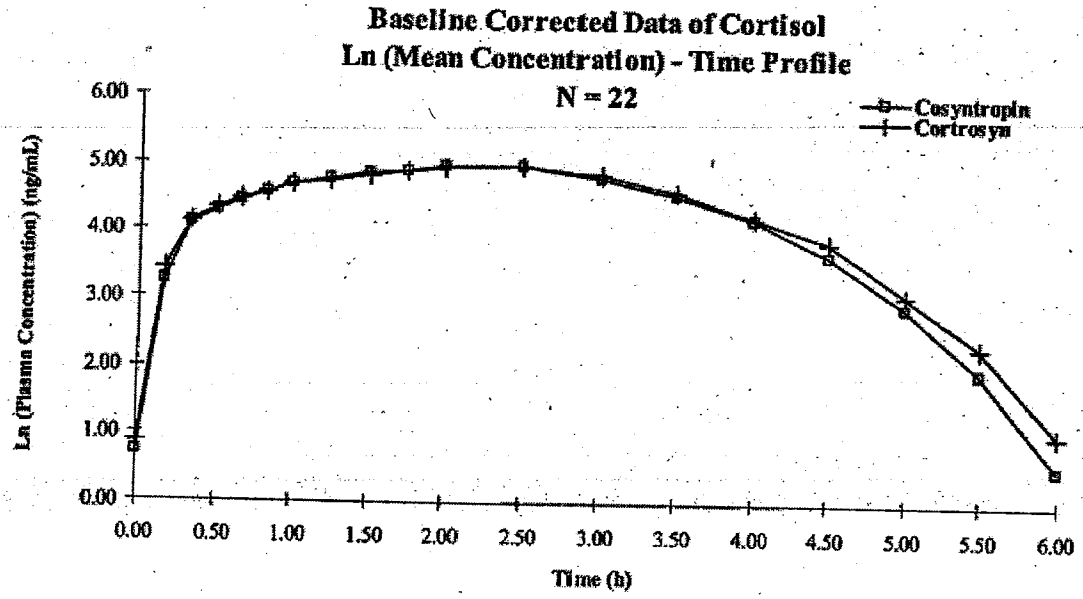
Pharmacodynamic Parameters

Parameter	Test [Cosyntropin A)]		Reference [Cortrosyn (B)]	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
$C_{30\ min}$ (ng/mL)	74.18±20.77	28.00	79.32±32.65	41.16
$C_{60\ min}$ (ng/mL)	107.82±30.17	27.98	107.98±40.03	37.07

Cosyntropin (A) vs Cortrosyn (B)

Parameter	C_{30} min	C_{60} min
Ratio	100.44%	105.93%
90% Geometric CI	83.67 – 120.58	92.68 – 121.08
Intra-subject CV	34.88%	26.01%


Baseline Corrected Data of Cortisol
Mean Concentration - Time Profile
N = 22
Cosyntropin
Cortrosyn
Plasma Concentration (ng/mL)
160
140
120
100
80
60
40
20
0
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
Time (h)


Baseline Corrected Data of Cortisol
Ln (Mean Concentration) - Time Profile
N = 22
Cosyntropin
Cortrosyn
Ln (Plasma Concentration) (ng/mL)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
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3.50
4.00
4.50
5.00
5.50
6.00
Time (h)

SUMMARY OF RESULTS
BASELINE UNCORRECTED DATA OF CORTISOL
N = 22

Pharmacodynamic Parameters

Parameters		Test (Cosyntropin (A)) Mean	±	SD	CV (%)	Reference (Cortrosyn (B)) Mean	±	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	1290.28	±	167.25	12.96	1277.72	±	157.25	12.31
C_{max}	(ng/mL)	295.46	±	36.39	12.32	291.70	±	33.54	11.50
T_{max}	(h)	2.31	±	0.55	23.63	2.27	±	0.39	17.28
T_{max}*	(h)	2.25	±	0.51	-	2.50	±	0.50	-

* Medians and interquartile ranges are presented.

Cosyntropin (A) vs Cortrosyn (B)

	AUC_{0-t}	C_{max}
Ratio[1]	101.02%	101.20%
90 % Geometric C.I.[2]	98.66 % to 103.44 %	98.67 % to 103.79 %
Intra-Subject CV	4.53 %	4.85 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Cosyntropin (A)} - \text{Cortrosyn (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data.

SUMMARY OF RESULTS OF ADDITIONAL ANALYSES
BASELINE UNCORRECTED DATA OF CORTISOL
N = 22

Pharmacokinetic Parameters

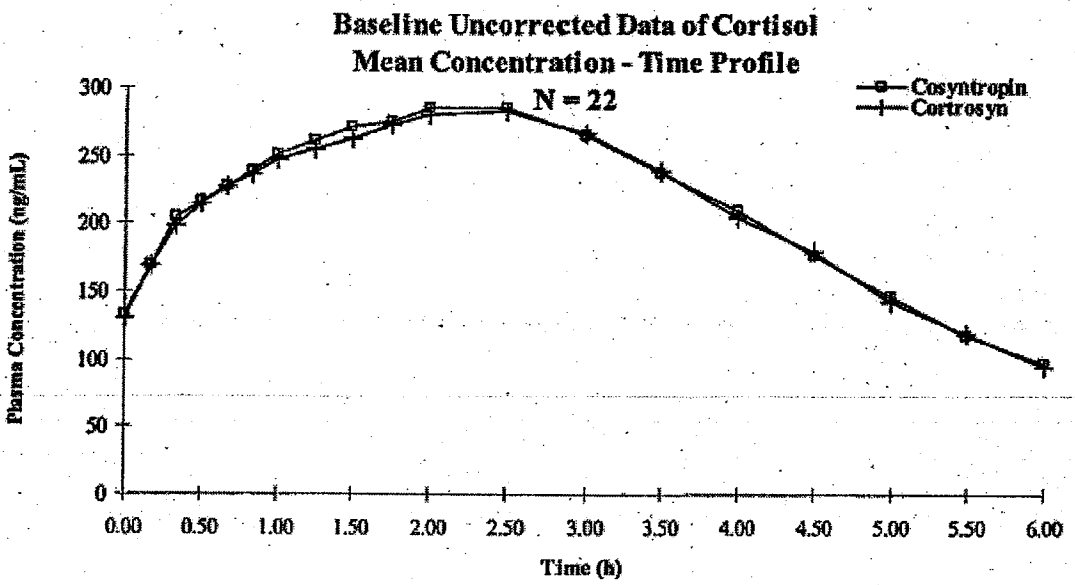
Parameters		Test (Cosyntropin (A)) Mean	±	SD	CV (%)	Reference (Cortrosyn (B)) Mean	±	SD	CV (%)
$C_{30\ min}$	(ng/mL)	215.07	±	26.35	12.25	214.76	±	29.06	13.53
$C_{60\ min}$	(ng/mL)	250.26	±	32.25	12.89	247.18	±	33.12	13.40

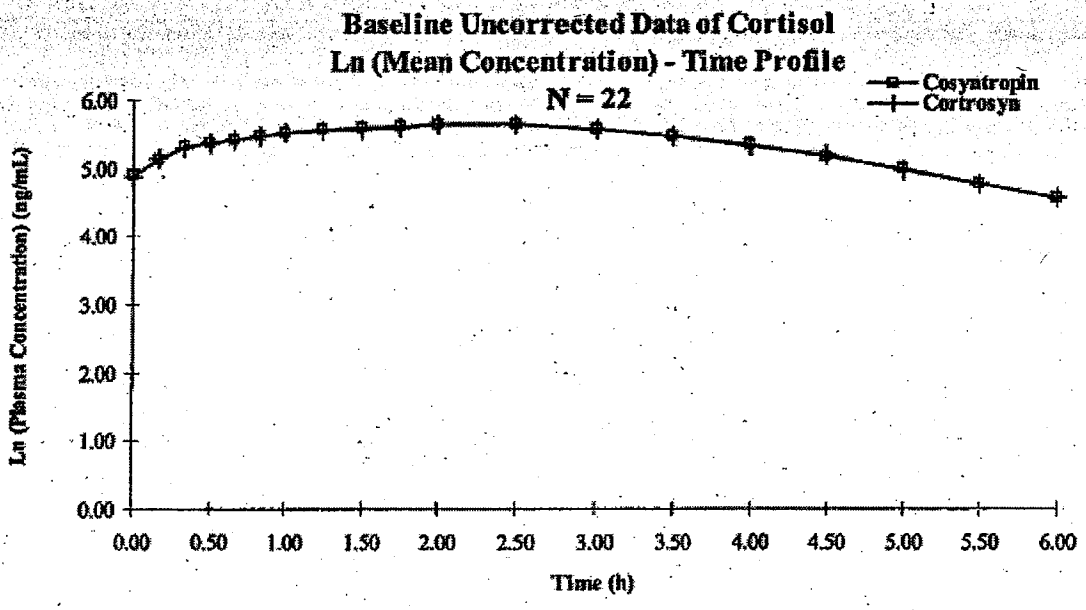
Cosyntropin (A) vs Cortrosyn (B)

	$C_{30\ min}$	$C_{60\ min}$
Ratio[1]	100.41%	101.42%
90 % Geometric C.I.[2]	97.22 % to 103.71 %	98.24 % to 104.70 %
Intra-Subject CV	6.20 %	6.10 %

[1] Calculated using least-squares means according to the formula: $e^{(\text{Cosyntropin (A)} - \text{Cortrosyn (B)})} \times 100$

[2] 90% Geometric Confidence Interval using ln-transformed data





Safety:

A total of 24 post-dose adverse events occurred during the study. Of these adverse events, 8 were judged to be unrelated to the study medication, resulting in a total of 16 potentially related adverse events. The number of potentially related adverse events experienced per treatment group is as follows: 9 adverse events following administration of treatment A and 4 adverse events following administration of treatment B. The remaining 3 adverse events were associated with clinically significant post-study laboratory tests and abnormal vital signs measurements and could not be assigned to a treatment group (date and time of onset is not known). No serious or significant adverse events were reported during this study. Upon conclusion of the clinical portion of the study, the results from the post-study laboratory tests and vital signs measurements confirmed the absence of significant changes in the subjects' state of health.

Conclusion:

Safety:

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

Pharmacodynamics:

Based on these results, it can be concluded that the cortisol response was comparable between the test cosyntropin (Treatment A) and the reference Cortrosyn (Treatment B) following 0.25 mg intravenous dose under fasting conditions when using the measures stated in the product monograph (i.e. C30min and C60 min). Moreover, the bioequivalence criteria set in the protocol were also met when excluding the non responding subject.

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/s/

Xiao-xiong Wei
12/1/2006 12:32:43 PM
BIOPHARMACEUTICS

Hae-Young Ahn
12/5/2006 03:56:41 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA Number	**22-028**	**Brand Name**	**N/A**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Cosyntropin injection**
Medical Division	**HFD-510**	**Drug Class**	**peptide**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Diagnosis of adrenal insufficiency**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**solution**
		Strength	**0.25 mg/mL**
Date of Submission	**02-06-2006**	**Route of Administration**	**SC**
Estimated Due Date of OCPB Review	**10-15-2006**	**Sponsor**	**Sandoz**
PDUFA Due Date	**12-06-2006**	**Priority Classification**	**S1**
Division Due Date	**11-01-2006**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**Yes**	
Comments sent to firm?	**No**	

Submission:

Sandoz Canada Inc. is seeking approval of Cosyntropin injection 0.25 mg/mL, aqueous formulation, based on the listed drug product, Amphastar's Cortrosyn™ for Injection 0.25 mg (lyophilized powder), which is identified in the Orange Book, "Approved Drug Products with Therapeutic Equivalence Evaluations" (NDA 16-750, CORTROSYN™).

CORTROSYN™ contains cosyntropin as the active ingredient, and is a sterile lyophilized powder for injection solely for administration by intramuscular and intravenous injection.

Sandoz 505(b)(2) NDA product, Cosyntropin Injection 0.25 mg/mL, has the same active ingredient in the same concentration and strength as the RLD with the exception of ingredients added to [redacted]. Sandoz Cosyntropin Injection 0.25mg/mL is formulated as a sterile aqueous solution [redacted]

b(4)

Product	Route of Administration	Dosage	Form
RLD Cortrosyn™ for injection	Intramuscular Intravenous	0.25 mg	0.25 mg lyophilized powder to be reconstituted with 1 mL 0.9 % NaCL
Sandoz Cosyntropin Injection	Intravenous	0.25 mg	0.25 mg/mL aqueous solution

Sandoz requests a therapeutically equivalent rating and TE code to the RLD (CORTROSYN™) upon approval of this application.

In order to demonstrate the bioequivalence between Sandoz Cosyntropin and the reference drug Cortrosin™, the sponsor conducted a BE study in 24 healthy subjects using PD parameters for cortisol as the primary markers. The sponsor used baseline corrected analysis as the primary method and baseline uncorrected analysis as a supportive method. The pharmacokinetic parameters were not analyzed.

The assay validation, QC study and PD datasets are submitted for review.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Xiao-xiong Wei
4/6/2006 04:10:02 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/7/2006 02:56:46 PM
BIOPHARMACEUTICS

Table 1. Summary of Bioavailability Studies baseline corrected data of cortisol

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$T_{½}$ (h)	K_{el} (h^{-1})	
50525	Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (Reference) Following a 0.25 mg Intravenous Dose in Healthy Subjects	Randomized, single-dose, 2-way crossover	Cosyntropin (1 mL x 0.25 mg/mL) injection i.v. Lot No.: 1200503-F	22 completing (13 males/9 females) Healthy subjects Age (years) = 37 (21-55) Weight (kg) = 71.5 (53.0-88.6) Data set for statistical analysis = 22	153.02 (38.90)	2.31 (0.55) 2.25 (0.51)*	470.39 (166.76)	480.69 (166.35)	0.46 (0.16)	1.7561 (0.8628)	Vol. # p.#
			Cortrosyn® (1 mL x 0.25 mg/mL) injection i.v. Lot No.: XC038E5		152.50 (50.88)	2.27 (0.39) 2.50 (0.50)*	481.19 (222.63)	504.30 (214.33)	0.69 (0.40)	1.1732 (0.3860)	

* Median (interquartile range)

Table 1. Summary of Bioavailability Studies baseline corrected data of cortisol

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)		Study Report Location
					$C_{30\ min}$ (ng/mL)	$C_{60\ min}$ (ng/mL)	
50525	Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (Reference) Following a 0.25 mg Intravenous Dose in Healthy Subjects	Randomized, single-dose, 2-way crossover	Cosyntropin (1 mL x 0.25 mg/mL) injection i.v. Lot No.: 1200503-F	22 completing (13 males/9 females) Healthy subjects Age (years) = 37 (21-55) Weight (kg) = 71.5 (53.0-88.6) Data set for statistical analysis = 22	74.18 (20.77)	107.82 (30.17)	Vol. # p.#
			Cortrosyn® (1 mL x 0.25 mg/mL) injection i.v. Lot No.: XC038E5		79.32 (32.65)	107.98 (40.03)	

Table 1. Summary of Bioavailability Studies baseline uncorrected data of cortisol

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$T_{½}$ (h)	K_{el} (h^{-1})	
50525	Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (Reference) Following a 0.25 mg Intravenous Dose in Healthy Subjects	Randomized, single-dose, 2-way crossover	Cosyntropin (1 mL x 0.25 mg/mL) injection i.v. Lot No.: 1200503-F	22 completing (13 males/9 females) Healthy subjects Age (years) = 37 (21-55) Weight (kg) = 71.5 (53.0-88.6) Data set for statistical analysis = 22	295.46 (36.39)	2.31 (0.55) 2.25 (0.51)*	1290.28 (167.25)	-	-	-	Vol. # p.#
			Cortrosyn® (1 mL x 0.25 mg/mL) injection i.v. Lot No.: XC038E5		291.70 (33.54)	2.27 (0.39) 2.50 (0.50)*	1277.72 (157.25)	-	-	-	

* Median (interquartile range)

Table 1. Summary of Bioavailability Studies baseline uncorrected data of cortisol

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route)	Subjects (No. M/F) Type, Age and Weight: mean (range)	Mean Parameters (SD)		Study Report Location
					$C_{30\ min}$ (ng/mL)	$C_{60\ min}$ (ng/mL)	
50525	Randomized, Open-Label, 2-Way Crossover, Bioequivalence, Pharmacodynamic Endpoint Study of Cosyntropin 0.25 mg/mL Injection and Cortrosyn (Reference) Following a 0.25 mg Intravenous Dose in Healthy Subjects	Randomized, single-dose, 2-way crossover	Cosyntropin (1 mL x 0.25 mg/mL) injection i.v. Lot No.: 1200503-F	22 completing (13 males/9 females) Healthy subjects Age (years) = 37 (21-55) Weight (kg) = 71.5 (53.0-88.6) Data set for statistical analysis = 22	215.07 (26.35)	250.26 (32.25)	Vol. # p.#
			Cortrosyn® (1 mL x 0.25 mg/mL) injection i.v. Lot No.: XC038E5		214.76 (29.06)	247.18 (33.12)	