CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: 202107

Drug Name: Corlux® (mifepristone)

Indication(s): To reduce the effects of hypercortisolism in patients with endogenous Cushing's syndrome

Applicant: Corcept Therapeutics

Date(s): 04/25/2011

Review Priority: Standard

Biometrics Division: 2

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Keywords:

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http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1. EXECUTIVE SUMMARY

The objective of this study was to examine the safety and efficacy of mifepristone for treatment of the signs and symptoms of hypercortisolemia in subjects with endogenous Cushing's syndrome from ACTH-dependent or ACTH-independent disorders.

This was a 24-week, open-label study of the administration of mifepristone to subjects with Cushing's syndrome. The sponsor states, "An open-label design was chosen for this study because of the lack of an approved comparator drug that was available commercially." Following a screening period of up to 6 weeks, 50 subjects were assigned to receive 300 mg mifepristone once daily (QD). Because the optimal dose of mifepristone for each subject was not known, dose escalation was undertaken cautiously with careful observation of clinical status. Dose escalations beyond 300 mg were made under some conditions.

Subjects belonged to one of two study cohorts. The C-DM cohort (n=29) consisted of subjects with Cushing's syndrome and diabetes or impaired glucose tolerance. The C-HT cohort (n=21) consisted of subjects with Cushing's syndrome and a diagnosis of hypertension only (without diabetes or impaired glucose tolerance). Each cohort had a separate primary efficacy endpoint.

The primary endpoint for subjects in **C-DM** was evaluation of response based on the change in AUC for glucose ($AUC_{glucose}$) from baseline to Week 24/ET for the 2-hour oGTT in the mITT population. A responder was a subject who had at least a 25% decrease in AUC from baseline. A response in $AUC_{glucose}$ was observed in 60% of the subjects (1-sided 95% CI lower bound, 42%). The sponsor considered this result to be statistically significant because the lower bound of the 95% CI was greater than 20%, the pre-specified margin of clinical significance. I also computed a 2-sided 95% confidence interval for the response rate. The lower bound of the 2-sided 95% confidence interval was 40.4%. The mean change from baseline in AUC was -8722 (2-sided 95% CI = (-13184, -4260), p=.0009) from a baseline mean of 30670.

	C-DM N=25 n (%)	Lower Bound 1-sided 95% Exact Binomial CI
Subjects who had at least a 25% decrease from baseline in $AUC_{glucose}$ at Week 24/ET		
Responder	15 (60.0)	41.68%
Non-responder	10 (40.0)	

HbA1c was not the primary endpoint in C-DM (it was a secondary endpoint) but nevertheless is an important clinical measure of diabetic control. The mean change from baseline in HbA1c was -1.11 (2-sided 95% CI = (-1.56, -0.65), p=.0001) from a baseline mean of 7.36. While it can be difficult to assess changes from baseline in $AUC_{glucose}$ and HbA1c in the absence of a control group, the observed changes were of sufficient magnitude so that they could be attributed to the action of the drug since hyperglycemia would be expected to persist without treatment and in the absence of significant fluctuations in cortisol and ACTH levels.

Nevertheless, clinical judgment should be given priority in this open-label study with titration and meager data.

The primary efficacy variable for subjects in **C-HT** was evaluation of response based on the change in diastolic blood pressure from baseline to Week 24. A responder was a subject who had at least a 5 mmHg reduction in dBP from baseline. A response for diastolic blood pressure was observed in 38% of the subjects (1-sided 95% CI lower bound, 21%). The sponsor considered this result to be statistically significant because the lower bound of the 95% CI was greater than 20%, the pre-specified margin of clinical significance. I also computed a 2-sided 95% confidence interval for the response rate. The lower bound of the 2-sided 95% confidence interval was 16.8% which fell below the margin.

	C-HT N=21 n (%)	**Lower Bound 1-sided 95% Exact Binomial CI**
Subjects who had at least a 5 mmHg reduction from baseline in diastolic blood pressure at Week 24/ET		
Responder	8 (38.1)	20.57%
Non-responder	13 (61.9)	

The mean change from baseline in dBP (mmHg) was -0.1 (2-sided 95% CI = (-4.6, 4.6), p=.98) from a baseline mean of 82.9. Therefore, across the two dBP endpoints, there was no statistical evidence of diastolic blood pressure lowering in the C-HT cohort.

Labeling

Though no statistical significance was claimed for the secondary efficacy variables, there is one danger that non-statisticians may not be fully alert that these descriptive statistics do not mean much. They are just numerical results based on one sample; there is no assurance or confidence regarding the population or the reality.

The definition of a Responder in the key secondary efficacy variable: "A responder was defined as a subject whose median reviewer score was + 1 at any reviewed visit after baseline through Week 24/ET" with the phrase "at any reviewed visit," gives multiple opportunities for a success and is not as dependable as a response at any one time-point. Therefore, the results of this key variable, if are allowed to be in the labeling at all, this point should be emphasized.

2. INTRODUCTION

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