Poster #GP158

Differentiated pharmacokinetics of levoketoconazole (COR-003), the single 2S,4R-enantiomer of ketoconazole, a new investigational drug for the treatment of Cushing's syndrome

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INTRODUCTION

- Endogenous Cushing's syndrome (CS) is a rare, serious, potentially lethal, endocrine disease caused by chronic, cortisol exposure[1]
- Ketoconazole, a 50/50 racemic mixture of the 2S,4R and 2R,4S enantiomers, is used to treat endogenous CS due to its inhibitory effect on adrenal steroidogenesis[2-4]
- COR-003 (levoketoconazole) is the 2S,4R enantiomer of ketoconazole
  - COR-003 has been shown to be a more potent inhibitor of cortisol synthesis than the 2R,4S enantiomer in vitro, in rats, and in healthy subjects[5]

OBJECTIVES

- To characterize the clinical pharmacokinetics (PK) of COR-003 and develop a PK model based on data from studies in healthy subjects and subjects with type 2 diabetes mellitus (T2DM)

METHODS

Clinical Studies

- Study 1 was a randomized, placebo-controlled, single-blind, 2-period, crossover, drug-interaction study in which healthy subjects (N = 18) received 400 mg of COR-003 or placebo once daily for 8 days and a single dose of 5 mg felodipine on Day 5; blood samples for the PK analysis of COR-003 and placebo were obtained for 24 hours after administration of felodipine
- Study 2 was a randomized, placebo-controlled, single-blind, 3-period, crossover, drug-interaction study in which healthy subjects (N = 24) received 400 mg of COR-003, 400 mg of racemic ketoconazole, or placebo once daily for 7 days and a single dose of 80 mg atorvastatin on Day 5; blood samples for PK analysis of COR-003, ketoconazole enantiomers, and placebo were obtained for 24 hours after administration of atorvastatin
- Study 3 was a phase 2a, double-blind, placebo-controlled, parallel-group study in which patients with T2DM (N = 37) received COR-003 at 200, 400, or 600 mg once daily; ketoconazole 400 mg once daily; or placebo for 14 days; blood samples for PK analysis of COR-003, ketoconazole enantiomers, and placebo were obtained for 24 hours on Days 1 and 14 after administration of study drugs

PK Analysis

- Plasma samples were assayed using a validated chiral assay for separate analysis of the 2 enantiomers
- Area under the curve (AUC), maximum concentration (C_{max}), and time to maximum concentration (T_{max}) were calculated using noncompartmental methods

PK Model Development

- Two separate models were developed for COR-003 (from Studies 1-3) and 2R,4S-ketoconazole (from Studies 1 and 2)
- Samples below the limit of quantitation (BLQ) were included when developing the model of 2R,4S-ketoconazole PK but not in the COR-003 model (due to the small number of BLQ samples)
- One-, 2-, and 3-compartment models with both linear and nonlinear clearance were evaluated; a 2-compartment model was the best fit for the data for both COR-003 and the 2R,4S-ketoconazole enantiomer
- An absorption lag was included
- Dose effects on clearance (CL), volume of distribution (V2), and absorption rate constant (KA) were evaluated and were not statistically significant for COR-003
  - A separate KA was estimated for Studies 1 and 2, given the potential drug interaction with felodipine and atorvastatin, respectively, compared with PK data from patients with diabetes
- Demographic information, including age, weight, and sex, was missing for several subjects from Study 3
  - These covariates were evaluated in the model but were not found to be statistically significant

RESULTS

PK of COR-003 in Studies 1 and 2

- In Studies 1 and 2, similar values for C_{max} (18,261 ng/mL and 11,147 ng/mL, respectively) and T_{max} (2.32 and 2.36, respectively) were seen for COR-003 (**Table 1**)
  - Exposure was highly variable

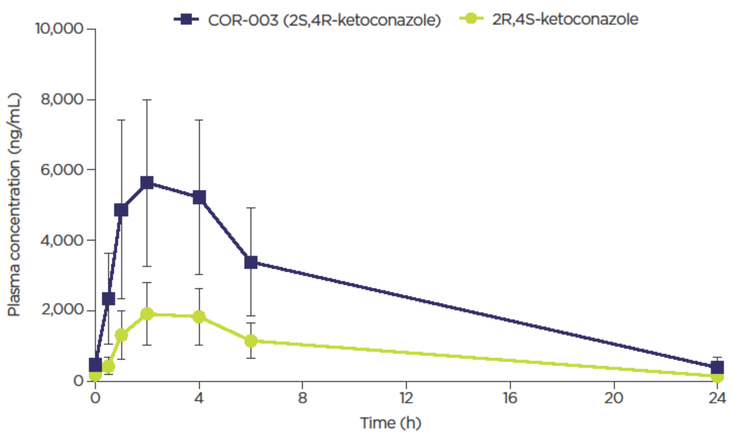
Table 1. PK Parameters of COR-003 Co-administered With Felodipine (Study 1) or Atorvastatin (Study 2) on Day 5

Study	Dose	Mean (CV) AUC, ng·h/mL	Mean (CV) C_{max}, ng/mL	Mean (CV) T_{max}, h
1	400 mg COR-003	175,223 (40.9%)	18,261 (42.3%)	2.32 (56.5%)
2	400 mg COR-003	114,195 (38.3%)	11,147 (36.7%)	2.36 (50.4%)

PK, pharmacokinetic; CV, coefficient of variation; AUC, area under the curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration.

Different Clinical PK of the 2 Ketoconazole Enantiomers

- In healthy subjects (Study 2), after 5 days of dosing with racemic ketoconazole, C_{max} of COR-003 was approximately 3-fold higher compared with the 2R,4S enantiomer (**Figure 1**)



*Enantiomer concentrations were evaluated from blood samples collected after 5 days of dosing with racemic ketoconazole.

Figure 1. Plasma concentration of COR-003 and 2R,4S ketoconazole over time in healthy subjects dosed with racemic ketoconazole (Study 2).*

- In subjects with T2DM (Study 3), after dosing with racemic ketoconazole on Day 1, exposure (C_{max} and AUC) of COR-003 was approximately 3-fold higher than that of the 2R,4S enantiomer (**Table 2**)

Table 2. Comparison of Enantiomer C_{max} and AUC Following Dosing of Racemate (Study 3)

	C_{max}, ng/mL			AUC_{0-24}, ng·h/mL		
Subject	COR-003	2R,4S	Ratio	COR-003	2R,4S	Ratio
1	5,030	1,720	2.92	31,216	11,116	2.81
2	6,830	2,620	2.61	39,901	15,749	2.53
3	5,490	1,780	3.08	25,584	8,903	2.87
4	5,320	2,050	2.60	23,547	9,656	2.44
5	5,060	1,960	2.58	25,427	11,397	2.23
6	5,790	1,930	3.00	34,419	12,012	2.87
7	1,380	456	3.03	10,491	4,116	2.55

C_{max}, maximum concentration; AUC_{0-24}, area under the curve from time 0 to 24 hours.

Safety and Tolerability of COR-003

- COR-003 was generally well tolerated in healthy subjects
  - In Study 1, the most frequently reported adverse events (AEs) were headache (94%), nausea (50%), and dizziness (44%)
    - All AEs were of mild to moderate intensity and no serious AEs were observed
    - No clinically significant changes in laboratory values were observed
  - In Study 2, headache (46%), back pain (17%), and nausea (17%) were the most frequently reported AEs
    - All AEs were of mild to moderate intensity and no serious AEs were observed
    - No clinically significant variations in liver function values were noted in the active treatment groups
- Overall, COR-003 was also safe and well tolerated in patients with T2DM
  - Headache (29%) and nausea (29%) were the most common AEs in subjects treated with COR-003
  - All AEs were of mild to moderate intensity; 1 subject experienced a serious AE (hyponatremia and urosepsis) that was deemed unrelated to study medication
  - No clinically relevant changes in hematology, blood chemistry, or urinalysis were observed in any of the treatment groups

PK Modeling

- A 2-compartment model with linear clearance was the best model for describing PK of both COR-003 and 2R,4S-ketoconazole
- Ketoconazole plasma elimination is biphasic: half-life is 2 hours during the first 10 hours and 8 hours thereafter[6]
  - Ketoconazole displays dose-dependent PK and half-life, with half-life increasing with long-term treatment[6]
- Estimated PK model parameters for COR-003 and 2R,4S-ketoconazole are shown in **Table 3**
  - In the 2R,4S-ketoconazole enantiomer model, a dose effect on KA and an allometric relationship between body weight and central volume were included

Table 3. PK Model Parameter Estimates of COR-003 and 2R,4S-ketoconazole

	COR-003		2R,4S-ketoconazole	
Parameter, units	Population mean (SE%)	% CV IIV (shrinkage)	Population mean (SE%)	% CV IIV (shrinkage)
CL, L/h	5.8 (9.3)	79.6 (3.7)	13.1 (13.5)	50.4 (3.7)
V2, L	48.9 (8.9)	70.7 (7.3)	103 (12.1)	40.5 (11.7)
Q3, L/h	1.25 (16.2)	–	0.102 FIX	–
V3, L	13,100 (11.8)	–	250 FIX	–
KA, 1/h	1.96 (13.7)	58.6 (29.0)	1.1 (21.8)	58.2 (22.8)
Absorption lag, h	0.344 (5.5)	–	0.426 (4.0)	–
Study 3 effect on KA	0.262 (20.3)	–	–	–
Dose effect on KA	–	–	0.101 (25.7)	–
Allometric body weight on V2	–	–	1 FIX	–
Residual variability	57.2 (6.0)	–	38.6% CV (2.6)	–

PK, pharmacokinetic; SE, standard error; CV, coefficient of variation; IIV, interindividual variability; CL, clearance; V2, central volume; Q3, intercompartmental clearance; V3, peripheral volume; KA, absorption rate constant; FIX, fixed values.

- As shown in **Figures 2** and **3**, PK models of COR-003 and the 2R,4S enantiomer demonstrated the following:
  - High residual variability and interindividual variability (IIV) in general
  - Acceptable precision of the parameter estimates
  - Estimates of clearance and volume were determined to be reflective of data from individual patients for both models, indicating that the model predicted individual parameters with precision

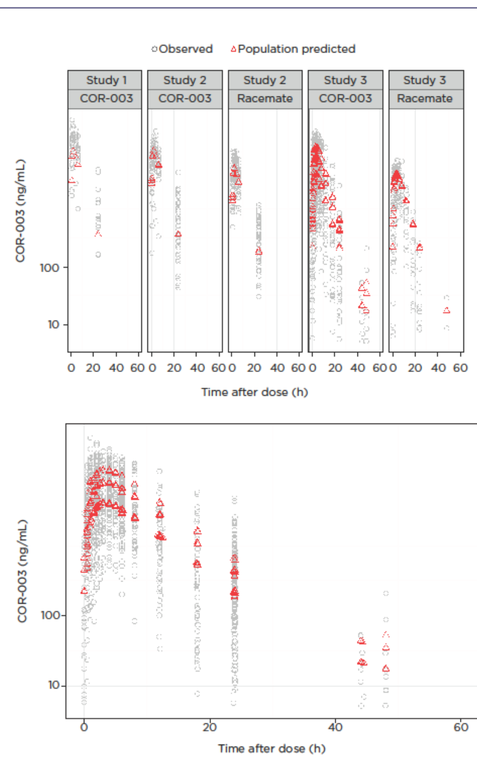


Figure 2. Observed versus population predicted concentrations of COR-003 over time (A) by study and (B) integrated for Studies 1 to 3.

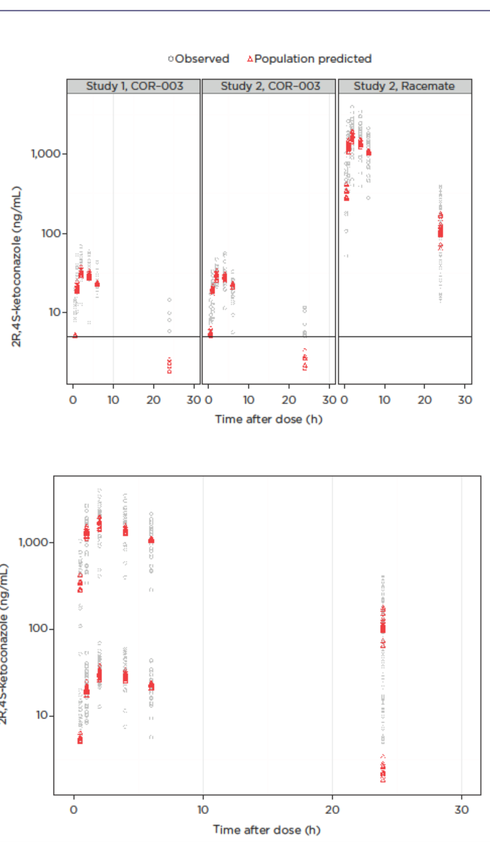


Figure 3. Observed versus population predicted concentrations of 2R,4S-ketoconazole over time (A) by study and (B) integrated for Studies 1 and 2.

SUMMARY

- Ketoconazole is a racemic 1:1 mixture of 2 enantiomers, 2S,4R- and 2R,4S-ketoconazole
- The 2S,4R enantiomer, COR-003 (levoketoconazole), is in phase 3 development for the treatment of endogenous CS due to its higher potency to inhibit adrenal cortisol synthesis
- After oral administration of racemic ketoconazole in healthy subjects in a drug interaction study, the plasma concentration of COR-003 in the presence of atorvastatin was approximately 3 times higher than the 2R,4S enantiomer
- Similarly, in a phase 2a study of patients with T2DM and in the absence of co-medication, the 2 ketoconazole enantiomers also exhibited differentiated PK
- PK modeling revealed a monophasic plasma-time curve for COR-003 compared with the biphasic pattern observed with ketoconazole
- PK modeling also revealed a greater clearance of 2R,4S-ketoconazole, which may indicate greater hepatic first-pass effect and liver exposure
- Ongoing mechanistic nonclinical studies will provide further insight into the differentiated PK profile of COR-003 and implications for hepatotoxicity and efficacy

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Acknowledgements

These studies were supported by Strongbridge Biopharma. Medical writing support was provided by Erica Chevalier-Larsen, PhD, of MedErgy, and was funded by Strongbridge Biopharma.

POSTER PRESENTED AT THE 18TH EUROPEAN CONGRESS OF ENDOCRINOLOGY (ECE); 28-31 MAY 2016; MUNICH, GERMANY.