

Coadministration of a CYP3A4 Inhibitor (Ketoconazole) Increased the Bioavailability of CS-7017 but Did Not Affect Tolerability: Results From an Open-label, Phase 1, Two-way Crossover Clinical Study in Healthy Subjects

G. Senaldi¹, H. Zahir¹, L. He¹, S.C. Rasmussen², K. Liu¹, R. Scheyer¹

¹Daiichi Sankyo Pharma Development (DSPD), Edison, NJ; ²Celerion Inc., Lincoln, NE; USA

BACKGROUND

- CS-7017 is a highly potent and selective peroxisome proliferator-activated receptor gamma (PPAR γ) agonist which has shown anticancer activity in preclinical cancer models.^{1,2}
- CS-7017 is currently in Phase 2 clinical development for the treatment of non-small cell lung cancer and colorectal cancer. In vitro data show that CS-7017 is metabolized by the CYP3A4/5 enzyme. Therefore, there is potential that CYP3A4 inhibitors may affect CS-7017 pharmacokinetics leading to increased exposure. During the course of their disease, cancer patients may receive multiple drugs, some of which may be CYP3A4 inhibitors. To ensure patients' safety, it is important to investigate the possible effect of CYP3A4 inhibitors on CS-7017 exposure.

OBJECTIVE

- To determine the effect of concomitant administration of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics and safety of CS-7017 in healthy subjects.

METHODS

Study design

- This was a phase 1, open-label, randomized, two-treatment, two-period, two-way crossover study.
- The protocol was approved by the Institutional Review Board, the study was conducted according to the Declaration of Helsinki, and all subjects provided informed consent.

Inclusion/exclusion criteria

- Healthy subjects aged 19–45 years with body mass index (BMI) values between 22 and 30 kg/m² were eligible for enrolment.

Treatments

- Subjects were randomized to receive two treatments:
 - Treatment A comprised a single oral dose of 0.25 mg CS-7017 on the morning of Day 4
 - Treatment B comprised an oral dose of 400 mg ketoconazole in the mornings of Days 1–6, and a single oral dose of 0.25 mg CS-7017 in the morning of Day 4

Treatment diagram

Sequence	Period 1	Washout	Period 2
1 AB	Treatment A	≥14 days	Treatment B
2 BA	Treatment B	≥14 days	Treatment A

End-points

- The primary end-points of this study were the ratios of the geometric means of the pharmacokinetic parameters of CS-7017 in combination with ketoconazole (Treatment B), relative to those of the pharmacokinetic parameters of CS-7017 administered alone (Treatment A).
- The safety and tolerability of CS-7017 with and without concomitant ketoconazole administration were also evaluated.

Statistical analysis

- Geometric mean and geometric coefficient of variation percentage were calculated for the area under the plasma concentration curve (AUC; AUC_{last} [AUC from the time of dosing to last measurable concentration], and AUC_{0-inf} [AUC from the time of dosing extrapolated to infinity]) and maximum (peak) observed plasma concentration (C_{max}).
- The ratio of geometric means (with two-sided 90% confidence interval [CI]) was used to calculate the difference between the two treatment groups.
- A mixed effect ANOVA model with treatment, period and sequence as fixed effects (factors) and subject nested within sequence as a random effect was performed on the *ln*-transformed C_{max} and AUC parameters of CS-7017.

RESULTS

Subject disposition and baseline demographics

- A total of 22 male subjects completed the study and were evaluable. Their baseline demographics are shown in Table 1.

Pharmacokinetics

- Concomitant administration of CS-7017 with ketoconazole:
 - significantly increased total exposure to CS-7017 by approximately 71%
 - extended the half-life of CS-7017 by 46%
 - did not significantly affect the C_{max} or time to maximum plasma concentration (t_{max}) of CS-7017 (Table 2)
- The plasma concentration–time curve shows that at each time point the mean CS-7017 concentrations were greater when CS-7017 was coadministered with ketoconazole (Treatment B) compared to when CS-7017 was administered alone (Treatment A) (Figure).

Safety

- There were no deaths, serious adverse events (AEs), or discontinuations due to AEs in this study.
- All treatment-emergent AEs were mild in severity.
- 10 subjects reported 17 AEs during the study. Only 2 treatment-emergent AEs (abdominal distension and abdominal discomfort) were considered to be related to study treatment (ketoconazole).

Table 1. Baseline demographics of the all-male subjects.

Characteristic	Sequence AB (n = 11)	Sequence BA (n = 11)	Overall (N = 22)
Race, n (%)			
Asian	2 (18.2)	0	2 (9.1)
Black	2 (18.2)	2 (18.2)	4 (18.2)
Caucasian	7 (63.6)	9 (81.8)	16 (72.7)
Ethnicity, n (%)			
Hispanic/Latino	1 (9.1)	2 (18.2)	3 (13.6)
Not Hispanic/Latino	10 (90.9)	9 (81.8)	19 (86.4)
Age, years			
Mean ± SD	27.5 ± 6.35	26.5 ± 2.70	27.0 ± 4.79
Median (range)	27.0 (20–40)	27.0 (23–31)	27.0 (20–40)
Height, cm			
Mean ± SD	173.8 ± 7.81	177.1 ± 6.11	175.5 ± 7.04
Median (range)	171.0 (162–184)	177.0 (166–187)	176.0 (162–187)
Weight, kg			
Mean ± SD	76.2 ± 8.56	82.3 ± 7.06	79.3 ± 8.27
Median (range)	73.7 (66.3–94.3)	82.7 (70.2–97.0)	77.9 (66.3–97.0)
BMI, kg/m²			
Mean ± SD	25.2 ± 2.00	26.3 ± 2.46	25.7 ± 2.26
Median (range)	24.7 (22.7–29.4)	26.4 (22.5–29.4)	24.9 (22.5–29.4)

SD, standard deviation.

Table 2. Pharmacokinetic parameters of CS-7017 with and without concomitant administration of ketoconazole.

Parameter	Geometric least-squares mean			90% CI
	CS-7017 alone (Treatment A)	CS-7017 plus ketoconazole (Treatment B)	Ratio B/A, %	
AUC _{last} (ng·h/mL)	193.4	330.4	170.81	161.57 to 180.58
AUC _{0-inf} (ng·h/mL)	214.3	367.5	171.48	161.62 to 181.94
C _{max} (ng/mL)	14.91	16.22	108.84	102.46 to 115.61
Median t _{max} (hours)	2.000	2.000	0.4917*	-0.008 to 0.983
Median t _{1/2} (hours)	10.504	15.305	6.0717*	5.213 to 6.749

*Hodges-Lehmann estimator for B/A.
AUC_{0-inf}, AUC from the time of dosing extrapolated to infinity, calculated as:
AUC_{0-inf} = AUC_{last} + C_{last}/λ_z; t_{1/2}, terminal half-life.

CONCLUSIONS

- Coadministration of ketoconazole significantly increased the bioavailability of CS-7017.
- Administration of a single dose oral dose of 0.25 mg CS-7017 either alone or concomitantly with 400 mg ketoconazole was well tolerated in healthy male subjects.
- CS-7017 MTD was not reached at the maximum tested phase 1 dose of 1.15 mg BID³, despite exposures comparable to those expected with CS-7017 0.5 mg BID administered with ketoconazole. Edema is the only dose-limiting toxicity observed with multiple dose of CS-7017 and is being clinically managed with diuretic therapy. Subjects requiring concurrent strong CYP3A4 inhibitors may receive the recommended Phase 2 dose of 0.5 mg BID.

References

- Copland JA, et al. Oncogene. 2006;25:2304-17.
- Shimazaki N, et al. Eur J Cancer. 2008;44:1734-43.
- Pishavaian MJ, et al. Presented at the 20th EORTC-NCI-AACR symposium 2008. Abstract number 409.

Acknowledgements

The authors would like to acknowledge editorial support provided by Remon van den Broek, PhD, and the team from Excerpta Medica.

Figure. Mean plasma concentrations of CS-7017 versus time of CS-7017 alone (Treatment A) or in combination with ketoconazole (Treatment B).

