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

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BACKGROUND
- CS-7017 is a highly potent and selective peroxisome proliferator-activated receptor gamma (PPARγ) agonist which has shown anticancer activity in preclinical cancer models.
- 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.

RESULTS

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), CMax (AUC from the time of dosing to last measurable concentration), and CMin (AUC from the time of dosing extrapolated to infinity) and maximum (peak) observed plasma concentration (CMax).
- The ratio of geometric means (with two-sided 90% confidence interval) 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 CMax and AUC parameters of CS-7017.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sequence AB (n = 11)</th>
<th>Sequence BA (n = 11)</th>
<th>Overall (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n, %)</td>
<td>Male (91)</td>
<td>Male (82)</td>
<td>Male (89)</td>
</tr>
<tr>
<td>Race, n (%</td>
<td>Caucasian (72)</td>
<td>Hispanic/Latino (9)</td>
<td>Not Hispanic/Latino (88)</td>
</tr>
<tr>
<td>Age, years</td>
<td>173.8 ± 7.8</td>
<td>177.1 ± 9.6</td>
<td>175.5 ± 9.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 ± 6.5</td>
<td>26.5 ± 7.7</td>
<td>27.0 ± 6.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.8 ± 8.1</td>
<td>177.1 ± 11</td>
<td>175.5 ± 10.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.2 ± 8.6</td>
<td>82.3 ± 9.6</td>
<td>79.3 ± 9.2</td>
</tr>
<tr>
<td>BML, kg/m²</td>
<td>2.7 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>2.9 ± 0.2</td>
</tr>
</tbody>
</table>

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).

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 BID, 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

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