DIFFERENTIAL EFFECTS OF CO-ADMINISTRATION OF RACEMIC KETOCONAZOLE AND LEVDEXKETOCONAZOLE ON THE PHARMACOKINETIC PROFILE OF ATORVASTATIN

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ABSTRACT

BACKGROUND: Racemic K1Z or its active mixture of 25R- and 25S-enantiomers, Levoketoconazole (L1KZ), or its 25R-enantiomer, is being developed as a novel corticosteroid synthesis inhibitor to treat hyperglycemia. A randomized, double-blind, placebo-controlled, phase 1b trial (NCT02320052) evaluated the impact of co-administration of AT1KZ or AT1ZK on the pharmacokinetics (PK) of AT1.

METHODS: 24 healthy adult volunteers (15 males and 9 females) between 18 and 55 years of age participated in the study.

RESULTS: The following drug interactions (drugs and substrates) were administered with 240 mg of water according to the randomization scheme:

- **Intestinally**: A 400 mg levoketoconazole tablets (3 x 200 mg tablets)
- **Substrates**: Subcutaneous injection of 5% AT1Z (1 x 1 mg tablets)

STUDY DESIGN

The study design is illustrated in Figure 1.

OBJECTIVES

**PRIMARY OBJECTIVE**

To evaluate the effects of multiple doses of a single administration of L1KZK, 25R-levo-ketoconazole, and the racemate, AT1, on plasma CYP3A4 activity, on the PKs of a single 80 mg dose of AT1 administered to healthy volunteers.

**SECONDARY OBJECTIVE**

To evaluate the safety and tolerability of concomitant multiple administrations of L1KZK, 25R-levo-ketoconazole, and the racemate AT1, both parent CYP3A4 substrates, on the PKs of a single 80 mg dose of AT1 administered to healthy volunteers.

RESULTS

- **PF samples were collected on Days 1, 4, 8, and 12 over 24 hours for the bioanalytical drug and drug metabolites across all studies.
- **Clinical assessments and adverse events were observed on Days 1 and 8.
- **Pharmacokinetic parameters were calculated using罗andShahokinetics Software.
- **Safety monitoring included vital signs, clinical laboratory tests, and physical examination.

CONCLUSION: Despite comparable inhibition of CYP3A4, the increased AUC of AT1 after L1KZ administration was less than AT1KZ and AT1. The increase in total exposure to pharmacologically active AT1-related compounds (parent AT1, 25R-AT1, 4-hydroxy-AT1) was significantly less for AT1KZ than for AT1.

**METHOD**

**TRIAL**: Single-dose, randomized, placebo-controlled, 3-way Cross-over Study

**SUBJECT POPULATION**: 24 healthy adult volunteers (15 males and 4 females) between 18 and 55 years of age participated in the study.

**DOSAGE**

- **Intestinally**: A 400 mg levoketoconazole tablets (3 x 200 mg tablets)
- **Substrates**: Subcutaneous injection of 5% AT1Z (1 x 1 mg tablets)

**STUDY DESIGN**

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