# Pharmacokinetics and Drug-Drug Interaction of Ocedurenone (KBP-5074) in Healthy Subjects

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**KBP BIOSCIENCES PTE. LTD.**

•Disclosures:

- **Ping Wang, Jinrong Liu, Judy Tan, Jay Zhang, Fred Yang are employees of KBP Biosciences**

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## ABSTRACT

**TITLE:**

**Pharmacokinetics and Drug-Drug Interaction of Ocedurenone (KBP-5074) in Healthy Subjects**

**BACKGROUND:**

**Ocedurenone, a novel non-steroidal mineralocorticoid receptor antagonist (MRA), is currently under development for the treatment of uncontrolled hypertension in patients with chronic kidney disease (CKD). Ocedurenone which is rapidly absorbed after oral administration has no or weak inhibition potential on major drug metabolizing CYP enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2C8. It is predominantly metabolized through CYP3A mediated pathways. Greater than 91% total oral dose is recovered in feces.**

**OBJECTIVES:**

**To determine the pharmacokinetic drug-drug interactions of Ocedurenone with CYP3A inhibitor itraconazole and inducer rifampin in healthy subjects.**

**METHOD:**

**This is a Phase 1, open-label, parallel, 2-arm, crossover study to investigate the effect of coadministration of a strong CYP3A4 inhibitor and CYP3A4 inducer on the plasma PK of a single dose of Ocedurenone in healthy male and female subjects. 24 subjects 18 to 60 years of age with a BMI of 18.0 to 32.0 kg/m2 were enrolled. Serial blood samples are collected from pre-dose through 240 hours post-dose for analysis of plasma concentrations of Ocedurenone.**

**RESULT:**

**The strong CYP3A inhibitor itraconazole and CYP3A inducer rifampin have statistically significant effects on the pharmacokinetics of Ocedurenone. Its $C_{max}$ and $AUC_{last}$ are increased to 110% and 170%, respectively, when itraconazole is co-administered. The median $t_{max}$ is slightly reduced from 4 hr to 2 hr. and the geometric mean $t_{1/2}$ is increased from 60.3 hr to 125 hr. When rifampin is co-administered, Ocedurenone $C_{max}$ and $AUC_{last}$ are significantly reduced to approximately 72% and 16%. Median $t_{max}$ was unchanged (4 hr), and the geometric mean $t_{1/2}$ is reduced to 10.9 hr.**

**CONCLUSION:**

**This clinical DDI study indicates that a strong CYP3A inhibitor (itraconazole) has a weak effect on Ocedurenone pharmacokinetic properties, with less than 2-fold change in $C_{max}$ and $AUC_{last}$; whereas a strong CYP3A inducer (rifampin) has strong effect on pharmacokinetic properties of Ocedurenone, with about 5-fold decrease in AUC and $t_{1/2}$. Ocedurenone was well tolerated when administered as a single 0.5-mg dose alone or in combination with itraconazole or rifampin.**

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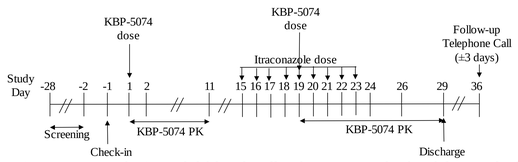
## BACKGROUND

- **Ocedurenone, a novel non-steroidal mineralocorticoid receptor antagonist (MRA), is currently under development, for the treatment of uncontrolled hypertension in patients with chronic kidney disease (CKD).**
- **Ocedurenone selectively binds to human mineralocorticoid receptor (MR) with higher affinity relative to glucocorticoid, progesterone, and androgen receptors compared to steroidal MRA such as spironolactone and eplerenone [1-3].**
- **The results of Ocedurenone phase 2 trial BLOCK-CKD indicate that Ocedurenone is an effective treatment option for stage 3b/4 CKD (eGFR 15-44m L/min/1.73m$^2$) patients with uncontrolled hypertension. Considering the lack of occurrence of hyperkalemia-related adverse events in terms of both frequency and severity, may be particularly useful for patients who are at risk for hyperkalemia [4].**

## METHOD

- **This clinical study employs a phase 1, open-label, parallel, 2-arm, crossover design to investigate the effect of coadministration of a CYP3A inhibitor (Cohort 1, itraconazole multiple dose) and CYP3A inducer (Cohort 2, rifampin multiple dose) on the plasma PK of a single dose of Ocedurenone in healthy male and female subjects. A total of 24 healthy male and female subjects between 18 and 60 years of age with a body mass index (BMI) between 18.0 and 32.0 kg/m$^2$ were selected according to the inclusion and exclusion criteria.**
- **For Cohort 1, study schematic is showed in Figure 1.**

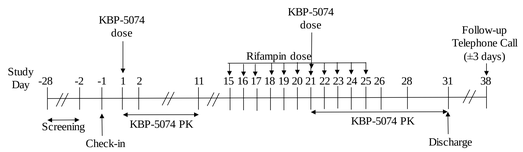
**Figure 1. Study Schematic – Cohort 1**




**On Days 1 and 19, serial blood collections were obtained for analysis of plasma concentrations of Ocedurenone.**

- **For Cohort 2, study schematic is showed in Figure 2.**

**Figure 2. Study Schematic – Cohort 2**




**On Days 1 and 21, serial blood collections were obtained for analysis of plasma concentrations of Ocedurenone.**

- **Safety was monitored with recording of AEs, clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis), vital sign measurements, 12-lead ECGs, and physical examination findings in all cohorts during the study.**

## RESULT

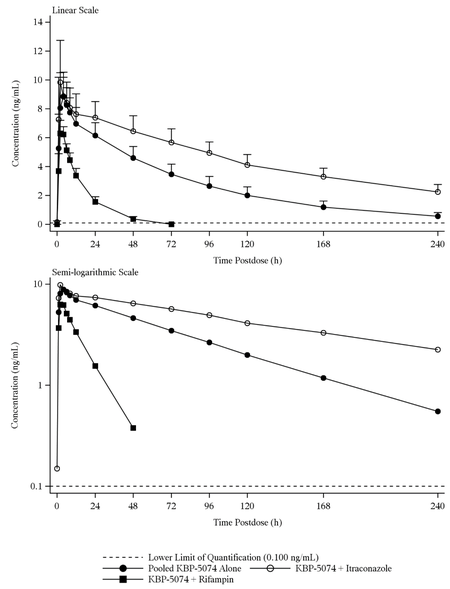
**Single oral doses of Ocedurenone appears to be safe and well tolerated when it is administered alone or in combination with itraconazole or rifampin to healthy subjects in this study. No TEAEs considered related to Ocedurenone were reported by any subjects during determination of the impact of multiple oral doses of itraconazole. Three (25.0%) of 12 subjects experienced 5 TEAEs, mild in severity, considered related to Ocedurenone during oral doses of rifampin. One subject experienced serious AE (SAE) of cholelithiasis and acute cholecystitis. The SAE was not related to Ocedurenone or rifampin. There were no clinically significant findings in the clinical laboratory evaluations, vital sign, 12-lead ECG, or physical examination data during the study.**

**For characterization of Ocedurenone single-dose PK, PK parameters for 0.5-mg alone treatment in Cohort 1 and 2 were pooled for summary statistics.**

**Co-administration of itraconazole significantly increased Ocedurenone plasma $AUC_{last}$, $AUC_{0-\infty}$, and $C_{max}$ to approximately 110% to 170%. However, the elimination $t_{1/2}$ is significantly increased from 60 hr to 125 hr , suggesting that itraconazole reduces CYP3A4/5-mediated clearance of Ocedurenone.**

**Co-administration of rifampin decreases Ocedurenone plasma AUC by approximately 84%, reduced its plasma $C_{max}$ by 28%, and $t_{1/2}$ is reduced to 11 hr, indicating that Ocedurenone metabolism/clearance is significantly enhanced in the presence of rifampin.**

**Figure 3. Arithmetic Mean (+SD) Plasma Concentrations of Ocedurenone Following**




**Single Oral Dose Administration of Ocedurenone 0.5 mg Alone (Day 1, Pooled) and in Combination with Itraconazole (Day 19, Cohort 1) and in Combination with Rifampin (Day 21, Cohort 2)**

**Table 1. Summary of Ocedurenone Pharmacokinetic Parameters Following Single Oral Dose of 0.5 mg in the Presence and Absence of Itraconazole and Rifampin Co-administrtaion**

| | Pooled Ocedurenone Alone | Ocedurenone+ Itraconazole | Ocedurenone+ Rifampin |
|---|---|---|---|
| **Parameter** | (N=24) | (N=12) | (N=11) |
| **$AUC_{last}$ (h*ng/mL)** | 640±21.4 | 1090±16.7 | 104±16.8 |
| **$AUC_{0-\infty}$ (h*ng/mL)** | 690±23.8 | 1410±20.0 | 109±16.5 |
| **$C_{max}$ (ng/mL)** | 9.14±18.2 | 10.1±23.2 | 6.57±11.3 |
| **$T_{max}$(h)** | 4 (2.00-6.00) | 2 (1.00-8.00) | 4 (2.00-4.00) |
| **$t_{1/2}$ (h)** | 60.3±20.4 | 125±13.8 | 10.9±13.9 |
| **CL/F (L/h)** | 0.725±23.8 | 0.355±20.0 | 4.61±16.5 |
| **Vz/F (L)** | 63.1±15.1 | 58.7±17.8 | 72.5±9.70 |

## CONCLUSION

- **Ocedurenone is well tolerated when administered as a single 0.5-mg dose, in the presence and absence of itraconazole and rifampin.**
- **Co-administration of a strong CYP3A4 inhibitor itraconazole slightly increased the Ocedurenone plasma exposures, $AUC_{0-tlast}$, $AUC_{0-\infty}$, and $C_{max}$ of Ocedurenone are increased approximately to 110% to 170%, while $t_{1/2}$ is increased from 60 hr to 125 hr.**
- **Co-administration of rifampin significantly decreases Ocedurenone plasma exposures, with $AUC_{0-tlast}$ and $AUC_{0-\infty}$, decreased to 16%; and $C_{max}$, decreased to approximately 72%.**

References

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