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Safety, Pharmacokinetics (PK), and Pharmacodynamics (PD) in Healthy Chinese Volunteers Treated with SC0062, a Highly Selective Endothelin-A (ETA) Receptor Antagonist

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Objectives : Endothelins (ET) play critical roles in vascular homeostasis and are implicated in various diseases, particularly chronic kidney disease (CKD). There are two main G-protein coupled ET receptors (ET_A and ET_B). SC0062 is a highly potent and selective ET_A antagonist in clinical development for CKD given the extensive data showing blockade of ET_A receptors is effective in reducing renal injury and proteinuria and inhibit inflammation and fibrosis, while blockade of ET_B receptors is associated with vasoconstriction and other unfavorable effects.
Methods : This study was comprised of single-ascending-dose (SAD), multiple-ascending-dose (MAD), and food-effect (FE) parts. The primary objectives were to characterize the safety, tolerability, and FE of SC0062. The secondary objectives were to determine the PK behavior of SC0062 and its major active metabolite M18, whereas exploratory objectives focused on PD effects, principally endothelin-1 (ET-1) and total bile acids (TBA).
Results : SAD of 10-100 mg and MAD of 20 and 50 mg daily for 6 days were well tolerated. SC0062 was rapidly absorbed and plasma exposure of SC0062 and M18 increased disproportionately with dose (Figure 1), achieving steady state by day 3 and accumulation ratios of 1.22 and 1.89 on day 6 for SC0062 and M18, respectively. The geomean (geoSD) $t_{1/2}$ of SC0062 and M18 were 7.25(1.70)h and 13.73(1.32)h, respectively. Plasma ET-1 concentrations were dose-proportional (Figure 2), whereas plasma TBA concentrations were somewhat erratic. The free drug concentrations of SC0062 and M18 at 20 mg daily were mostly above the IC_{50} of ET_A inhibition throughout the entire dosing interval. Following a single 50 mg dose after a high-fat meal, C_{max} values for SC0062 and M18 increased approximately 41% and 32%, respectively, and median T_{max} for SC0062 was 3 hours longer than fasting values, whereas exposure was unaffected.
Conclusions : The favorable safety, PK, and PD results provide a foundation for further studies of SC0062 in CKD.

Figure 1. PK Profile of SC0062 and M18 in SAD and MAD Cohorts.png

Figure 1. Mean (Standard Deviation) plasma concentration-time profiles (semi-log) as a function of SC0062 dose in the SAD and MAD studies. (a) Profiles of SC0062 in the SAD study; (b) Profiles of M18 in the SAD study; (c) Profiles of SC0062 in the MAD study; (d) Profiles of M18 in the MAD.
Abbreviations: MAD, multiple ascending dose; n, number of subjects; and SAD, single ascending dose.

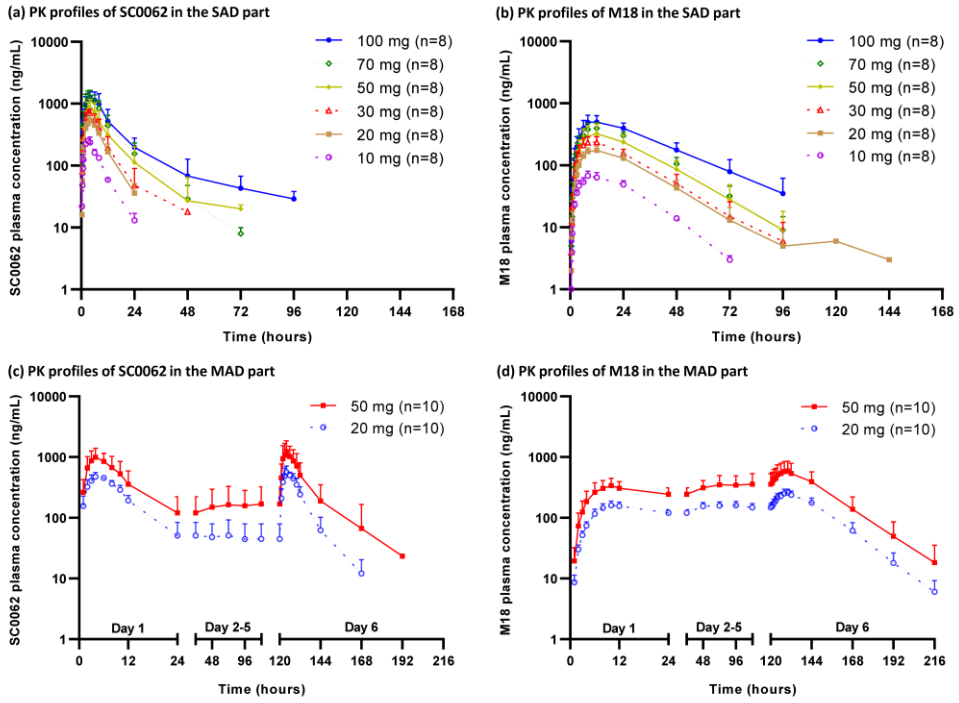

Figure 1. PK Profile of SC0062 and M18 in SAD and MAD Cohorts.png

Figure 2. $AUEC_{0\text{-}24h}$ values (standard deviation) of plasma ET-1 and AUC_{tau} values (standard deviation) of SC0062 and M18 (lines) as a function of the SC0062 dose level in the MAD part of the study.
Abbreviations: AUC_{tau}, area under the plasma concentration-time curve during a dosage interval; $AUEC_{0\text{-}24h}$, area under the plasma ET-1 concentration-time curve from time zero to 24 hour; MAD, multiple ascending dose.