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Single-dose Pharmacokinetics of Extended-release Calcifediol (ERC) in Healthy Japanese and Non-Japanese Volunteers

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INTRODUCTION

Extended-release calcifediol (ERC) is currently approved in the United States (US) and certain European countries at a daily dose of 30 µg escalating, as needed, to 60 µg for the treatment of secondary hyperparathyroidism in patients with non-dialysis chronic kidney disease. This study examined, for the first time, racial differences in pharmacokinetic (PK) profiles of serum calcifediol and its primary metabolites after oral doses of ERC.

AIM

To compare fasting and fed PK profiles of serum calcifediol and its metabolites after single oral doses of ERC to US adult Japanese (first-generation) and non-Japanese volunteers.

METHOD

Single oral ERC doses of 450, 900 or 1,800 µg (fasting) or 900 µg (fed) were administered to healthy Japanese (n=35) and non-Japanese (n=32) volunteers according to a randomization plan ensuring gender balance. Participants were housed in a US Phase 1 unit for 2 days prior to and post dosing, received standardized and timed meals, and provided blood samples at pre-dose baseline and post-dose at 2-hour intervals through 24 hours with decreasing frequencies thereafter through 28 days. Collected samples were analyzed for serum calcifediol, 24,25-dihydroxyvitamin D_3 ($24,25D_3$), total 1,25-dihydroxyvitamin D (1,25D), corrected calcium (Ca) and phosphorus (P).

RESULTS

Three participants were excluded from analysis for major protocol deviations. The median time to reach maximum post-dose serum calcifediol concentrations (t_{max}) was 9 to 28 hours (fasting) and 9 hours (fed) in both Japanese and non-Japanese participants. Median baseline-adjusted maximum concentration (C_{max}) and area under the curve ($AUC_{0\text{-last}}$) rose progressively (but not proportionally) with increasing dose in the fasting condition, and were approximately 5- and 3-fold higher, respectively, under fed conditions irrespective of race. Geometric mean ratios for $AUC_{0\text{-last}}$ were close to unity after adjustment for body weight. Median terminal elimination half-life ($t_{1/2}$) ranged from 9.4 to 17.6 days and tended to lengthen with increasing dose. Serum 1,25D reached maximum levels on Day 3 then decreased to near baseline levels by Day 7 for both races, and the increases were greater under fed compared to fasting conditions. Serum $24,25D_3$ concentrations were elevated between Days 1 and 28, and were comparable under fasting and fed conditions for both races. Serum Ca and P remained constant after all doses and treatment-emergent adverse events were all mild and unrelated to treatment.

CONCLUSIONS

Similar PK profiles of serum calcifediol and its primary metabolites ($24,25D_3$ and 1,25D) were observed between US Japanese (first generation) and non-Japanese participants after single oral ERC doses in fasting or fed conditions.

Table 1: Baseline Characteristics and Post-dose Calcifediol Data by Dose and Race

Parameter (n)	450 µg – Fasted J (8)	450 µg – Fasted Non-J (8)	900 µg – Fasted J (8)	900 µg – Fasted Non-J (8)	1800 µg – Fasted J (8)	1800 µg – Fasted Non-J (8)	900 µg – Fed J (8)	900 µg – Fed Non-J (8)
Baseline								
Age (years) Mean±SD	40±11	41±7	41±8	45±7	35±9	42±7	35±8	40±9
Gender (n) Male	4	4	4	3	5	3	6	3
BMI (kg/m²) Median	21.4	26.9	22.8	26.1	22.7	27.2	22.6	25.0
25OHD (ng/mL) Mean±SD	22±9	26±7	24±9	28±6	25±10	28±7	23±8	26±8
Post-Dose								
t_{max} (h) Median	24	15	22	28	9	16	9	9
C_{max} (ng/mL) Median	11.6	16.3	32.5	21.0	51.5	44.2	143.9	102.8
$t_{1/2}$ (h) Median	225	297	298	338	336	422	312	389
$AUC_{0\text{-last}}$ (h*ng/mL) Median	4,492	4,779	8,834	6,808	12,953	11,888	25,526	20,905
GMR (90% CI)	0.66 (0.47,0.93)		1.05 (0.74,1.49)		1.05 (0.74,1.49)			

J=Japanese; BMI=body mass index; 25OHD=25-hydroxyvitamin D; SD=standard deviation; BMI=body mass index; GMR=geometric mean ratio of Japanese/Non-Japanese adjusted for body weight; CI=confidence interval.

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