OPEN LABEL, PLACEBO-CONTROLLED, RANDOMIZED, SINGLE DOSE ESCALATION AND REPEAT DOSE STUDY OF INTRAVENOUS CTA018 IN HEALTHY VOLUNTEERS.

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Vitamin D hormone analogs are commonly used to treat secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) patients, but are often associated with hypercalcemia and hyperphosphatemia.

CTA018 is a novel vitamin D analog with dual mechanism of action: 1) it binds to vitamin D receptors, which activate vitamin D signaling pathways and 2) it inhibits 24-hydroxylase (CYP24), the enzyme that inactivates vitamin D.

This study evaluated the safety, pharmacokinetic (PK) and pharmaco-dynamic (PD) profile of intravenous CTA018 in healthy volunteers. During (Stage I) the single-dose phase, CTA018 or placebo was administered every 4 days to 10 (7 active: 3 placebo) healthy volunteers at doses of 10µg, 30µg, 60µg, 90µg, 120µg, 150µg and 180µg. Two doses, 90µg and 180µg, were selected for repeat administrations in Stage II; in both groups, 10 (8 active: 2 placebo) volunteers received intravenous CTA018 or placebo 5 times over 10 days.

In Stage I, none of the doses administered affected Ca, P or PTH. In Stage II, no significant differences in t_{max}, $T_{½}$, Vd and clearance were observed between the two doses. There was no accumulation of CTA018, most likely due to a short elimination half-life of ~2 hours. In the 180µg dose group, mean and median plasma iPTH levels were reduced over 20%, which was clinically significant. No increase in serum or urine Ca or P was observed. In the 90µg and 180µg groups, the median $25(OH)D_3$ levels increased by 27% and 63% respectively from baseline, compared to 6% increase in the placebo group. There were no deaths or serious adverse events and primary safety parameters (chemistry, hematology and urinalysis) were comparable between placebo and CTA018 treated groups.

In healthy volunteers, intravenous CTA018 was observed to be safe up to a dose of 180µg, which reduced iPTH without affecting Ca or P. The observed increase in $25(OH)D_3$ levels may suggest that CTA018 reduces CYP24-mediated catabolism of $25(OH)D_3$.