SAFETY, TOLERABILITY AND PHARMACOKINETICS OF CTP-499 IN A MULTI-CENTER, DOUBLE-BLIND, TWO-ARM, PLACEBO-CONTROLLED, RANDOMIZED STUDY IN NON-DIALYSIS PATIENTS WITH STAGE 3 CHRONIC KIDNEY DISEASE

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Study Design

- **Study Design**
  - CTP-499 is a new chemical entity in clinical development.
  - CTP-499 was supplied as 200 mg controlled-release tablets.
  - Matching placebos were available.

Results

- **Results**
  - A total of 25 patients with stage 3 CKD were randomized to CTP-499 and 8 patients were randomized to placebo, with 23 (92.0%) and 8 (100.0%) patients completing the 4-week treatment period, respectively.

Safety & tolerability

- **Safety & tolerability**
  - All patients succeeded in titrating to BID dosing after 2 weeks of QD dosing
  - All AEs were mild
  - No SAEs were reported
  - Most common AE was nausea, generally transient
  - No significant abnormalities in vital signs, labs, ECGs, or PE

Pharmacokinetics

- **Pharmacokinetics**
  - The plasma concentration time profiles for CTP-499 after the first and last dose are shown in Figure 1. Accumulation in AUC of 1.3 to 1.5X for CTP-499 and its metabolites was observed after two weeks of BID dosing (Figure 2). Exposure to CTP-499 and the metabolites M1 and M2 showed no apparent dependence on the degree of renal function. Exposure to the renally-excreted metabolites M4 and M5 increased slightly with declining renal function. At steady-state, 52% of the administered dose was found in the urine as CTP-499 or its metabolites, with the large majority being M5 (Figure 3).

Conclusions

- CTP-499 administered 600 mg BID was well tolerated in stage 3 CKD patients – no safety signals were identified
- Upon repeat dosing of CTP-499 in CKD patients, modest accumulation of the parent compound and its metabolites was observed
- The majority of the urinary excretion was in the form of the M5 metabolite
- The results of this trial support the use of a 600 mg BID regimen in an ongoing phase 2 study in diabetic nephropathy patients

Materials & Methods

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  - CTP-499 was supplied as 200 mg controlled-release tablets. Matching placebos were available.

Study Design

- **Study Design**
  - Key Inclusion Criteria: eGFR 30-59 mL/min/1.73 m², non-smoker, BP <160/95
  - Serial plasma and urine sampling following first and last dose on Days 1 and 28
  - Drug was administered in the fasted state

Safety and Tolerability

- The incidence and frequency of adverse events were assessed.
- Descriptive statistics were used to summarize, by Treatment Group, the absolute values and changes from baseline for safety and tolerability endpoints.
- No SAEs were reported
- Most common AE was nausea, generally transient
- No significant abnormalities in vital signs, labs, ECGs, or PE

Pharmacokinetic Analysis

- CTP-499 and its metabolites (M1-M5) were analyzed by HPLC-MS/MS methods. Plasma PK parameters, including Cmax, Tmax, AUC0-24, AUC0-t, C0-t, Cmax0-t, T1/2, CL/F, V/F and Ka, were estimated by using WinNonlin via non-compartmental methods. Amounts excreted in the urine at predetermined intervals were calculated.

Conclusions

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