SINGLE ASCENDING DOSE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF CTP-499, A NOVEL AGENT BEING INVESTIGATED FOR TREATMENT OF CHRONIC KIDNEY DISEASE

Introduction

CTP-499 is an analog of 1-(5)-5-hydrox(y)ethyl)-3,7-dimethyloctamine (HDX), an active metabolite of pentoxifylline (PTX), in which several key hydrogen atoms have been replaced with deuterium in order to provide improved metabolic stability. CTP-499 and HDX have similar physical, chemical, and pharmacological properties.

The first human study with CTP-499 investigated three different controlled-release formulations and Trental®, a controlled-release formulation of pentoxifylline (PTX), using a four-way cross-over design. PTX, which is believed to have complex mechanisms of action including hemorheologic, anti-inflammatory, anti-fibrotic, and immunomodulatory effects, has been reported in preliminary studies to have beneficial effects on proteinuria and renal function decline1-3. Trental is approved in the US for the treatment of intermittent claudication on the basis of chronic occlusive arterial disease of the limbs.

The results of the first human study showed that the medium release-rate formulation of CTP-499 forms the same metabolites as PTX however, compared to Trental, exposure to species possessing anti-inflammatory, anti-fibrotic, and immunomodulatory effects was increased while plasma levels for the renally eliminated M5 metabolite were decreased. This profile makes CTP-499 a unique potential treatment for diabetic nephropathy.

Materials and Methods

Study Design

CTP-499 was supplied as a 200 mg CR tablet, and was a 400 mg IR capsule.

Study Design

Part A:
- Double blind, placebo-controlled, single ascending dose administration of four oral doses of CTP-499 CR under fasting conditions.
- Eight healthy male volunteers aged 18 – 55 years per dose group randomized 3:1 drug:placebo.
- Doses: 600, 1200, 1800 and 2400 mg as controlled-release tablets

Part B:
- 6 subjects received a single oral dose of a 400 mg IR capsule of CTP-499 under fasting conditions.

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 clinical laboratory evaluations, vital signs and ECG findings.

Pharmacokinetic Analysis

After discrete CTP-499 and PTX doses, human plasma samples were collected for the measurement of pharmacokinetic parameters. CTP-499, PTX, and their respective metabolites were analyzed by validated HPLC-MS/MS methods. PK parameters, including Cmax, Tpeak, AUC0-t, AUC0-∞, V/F, t1/2, and k0 were estimated by using WinNonlin via non-compartmental methods.

Conclusions

- CTP-499 is a novel deuterium-containing compound in clinical development for CKD
- Controlled-release tablets were well-tolerated at single doses up to and including 1800 mg
- Cmax and AUC of CTP-499 increased approximately in proportion to dose across the range of tolerated doses
- PK and safety outcomes indicate the potential for once-daily dosing
- Concert expects to initiate a 6 month proof-of-concept study in diabetic nephropathy patients early in 2012 (see Abstract P195)