# P666: PHARMACOKINETIC AND SAFETY PROFILE OF CTP-692 (DEUTERATED D-SERINE) FOLLOWING ADMINISTRATION OF SINGLE AND MULTIPLE ASCENDING DOSES IN HEALTHY VOLUNTEERS

Vinita Uttamsingh, Emily McIntyre, Sunanda Vedananda, Christopher L Brummel, Virginia Braman, James V Cassella.
Concert Pharmaceuticals, Inc.

## Introduction

CTP-692 is a deuterated analog of D-serine, an endogenous co-agonist for the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor. Glutamatergic hypofunction is involved in the pathophysiology of neuropsychiatric disorders, including schizophrenia. Treatment with D-serine in patients with schizophrenia has been reported to result in improvement in positive and negative symptoms and cognitive dysfunction.

A potential limitation to the development of D-serine as a therapeutic is that it has been shown to cause nephrotoxicity in rats and, at high doses, has been associated with proteinuria in human studies. In preclinical studies conducted by Concert, D-serine-induced nephrotoxicity in rats, reflected by significant increases in blood urea nitrogen (BUN) and serum creatinine, at doses consistent with those reported in the literature. However, rats treated with CTP-692 over the same dose range exhibited BUN and serum creatinine levels in the normal range, suggesting a potentially improved renal safety profile.

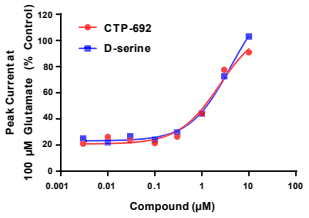
The *in vitro* binding and functional activity of CTP-692 at the glycine modulatory site of the NMDA receptor are nearly identical to those of D-serine. In other preclinical studies it was observed that CTP-692 distributes preferentially to the rat forebrain (forebrain/plasma ratio > 5) with substantially higher exposure compared to D-serine.

This poster presents the PK and safety profile of CTP-692 in single-and multiple-ascending dose studies. In these studies, CTP-692 had a well-defined PK profile with lower variability than has been previous described for D-serine (Tsai GE et al., J Clin Pharmacol, 2008, 48: 524). The drug was generally well tolerated supporting the development of CTP-692 as a potential new once-daily therapy for the adjunctive treatment of schizophrenia.

## CTP-692 and D-Serine have Similar Pharmacological Properties

Nearly identical binding and activation of the NMDA receptors by CTP-692 and D-serine (automated patch clamp system using HEK293 cells expressing human NMDAR subunits GluN1 and GluN2A).

**Representative NMDAR Activation Curves for CTP-692 and D-Serine**




| Drug Dosed | $ED_{50}$ (µM) |
|---|---|
| CTP-692 | 1.3 |
| D-Serine | 1.6 |

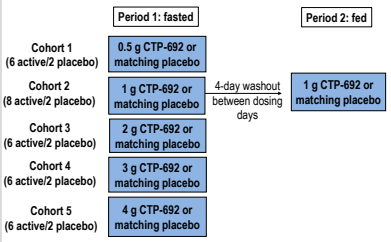
## For further information

Please contact:
vuttamsingh@concertpharma.com

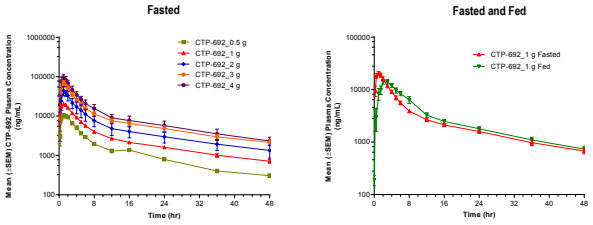
## Single Ascending Dose (SAD) Study

CTP-692 was administered orally as a solution after an overnight fast (Period 1) or within 30 minutes of consumption of a meal (Period 2). The safety and PK profile of single doses of CTP-692 were evaluated.

**SAD Study Design**




**CTP-692 Plasma Concentration Profile**




**Treatment-Related Adverse Events**

| Adverse Event (AE) | CTP-692 Dose | | | | | Placebo |
|---|---|---|---|---|---|---|
| | 0.5 g | 1 g | 2 g | 3 g | 4 g | |
| **Number of Patients: AE/ Total** | 1/6 | 3/8 | 1/6 | 1/6 | 0/6 | 2/10 |
| Headache | 1 | 2 | 1 | 1 | 0 | 1 |
| Nightmares | 0 | 1 | 0 | 0 | 0 | 0 |
| Fogginess, metallic taste, irritability | 0 | 0 | 1 | 0 | 0 | 0 |
| Abdominal pain, nausea, vomiting | 0 | 0 | 0 | 1 | 0 | 0 |
| Tiredness | 0 | 0 | 0 | 0 | 0 | 1 |
| Mental fogginess | 0 | 0 | 0 | 0 | 0 | 1 |

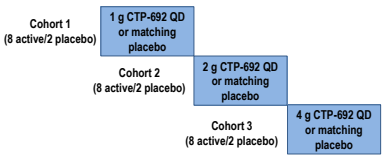
**CTP-692 Plasma PK Parameters**

| CTP-692 Dose | Median (range) | Arithmetic Mean (CV%) | | | |
|---|---|---|---|---|---|
| | $t_{max}$ (hr) | $C_{max}$ (µg/mL) | $t_{1/2}$ (hr) | $AUC_{\infty}$ (µg*hr/mL) | CL/F (L/hr) |
| 0.5 g | 1.0 (0.5 – 1.5) | 11.0 (26%) | 15.9 (9%) | 82.2 (13%) | 6.17 (13%) |
| 1 g | 1.0 (0.5 – 1.5) | 22.3 (21%) | 19.2 (22%) | 164 (18%) | 6.28 (17%) |
| 1 g (fed) | 2.0 (1.0 – 4.0) | 15.3 (30%) | 17.9 (17%) | 173 (21%) | 5.99 (19%) |
| 2 g | 1.0 (0.5 – 1.5) | 46.3 (20%) | 20.2 (22%) | 315 (21%) | 6.56 (19%) |
| 3 g | 1.0 (0.5 – 2.0) | 69.1 (41%) | 20.6 (9%) | 489 (27%) | 6.68 (31%) |
| 4 g | 1.0 (0.5 – 1.0) | 96.5 (19%) | 18.4 (15%) | 618 (21%) | 6.69 (20%) |

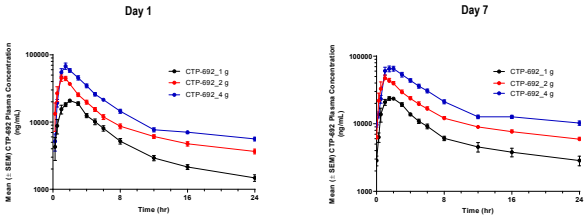
## Multiple Ascending Dose (MAD) Study

CTP-692 was administered orally as a solution for 7 consecutive days and within approximately 1 hour of consumption of food. The safety and PK profile of single doses of CTP-692 were evaluated.

**MAD Study Design**




**CTP-692 Plasma Concentration vs Time Profile**




**Treatment-Related Adverse Events**

| Adverse Event (AE) | CTP-692 Dose | | | Placebo |
|---|---|---|---|---|
| | 1 g | 2 g | 4 g | |
| **Number of Patients: AE/ Total** | 5/8 | 2/8 | 0/8 | 1/6 |
| Headache | 3 | 2 | 0 | 0 |
| Eructation, gastric upset | 1 | 0 | 0 | 0 |
| Dry mouth | 1 | 0 | 0 | 0 |
| Sleepiness/drowsiness | 1 | 1 | 0 | 0 |
| Loose stool | 0 | 0 | 0 | 1 |

**CTP-692 Day 7 Plasma PK Parameters**

| CTP-692 Dose | Median (range) | Arithmetic Mean (CV%) | | |
|---|---|---|---|---|
| | $t_{max}$ (hr) | $C_{max}$ (µg/mL) | $AUC_{0\text{-}24hr}$ (µg*hr/mL) | $AUC_{\infty}$ (µg*hr/mL) |
| 1 g | 1.5 (0.5-3.0) | 25.3 (12%) | 175.4 (23%) | 263.2 (30%) |
| 2 g | 1.0 (0.25-2.0) | 52.0 (23%) | 332.6 (11%) | 521.9 (19%) |
| 4 g | 2.0 (1.0-4.0) | 70.8 (26%) | 539.1 (14%) | 911.4 (19%) |

## Conclusions

### CTP-692 Safety:

1. CTP-692 was well-tolerated in the SAD and MAD studies
2. The most common treatment-related adverse event was headache
3. There were no CTP-692-related trends in the occurrence of headaches
4. All adverse events were mild to moderate in severity and recovered/resolved by the end of the study
5. In both studies, no CTP-692-related adverse events were reported at the highest once-daily dose of 4 g
6. All serum and urine kidney function parameters remained within the normal range in both studies
7. There were no clinically significant CTP-692-related effects on other clinical laboratory parameters
8. No evidence of adverse effects on neurocognitive functioning (CogScreen)

### CTP-692 PK:

1. CTP-692 had a well-defined PK profile with low inter-individual variability
2. The CTP-692 dose-exposure relationship was linear following single and multiple doses (at Day 7)
3. The terminal $t_{1/2}$ of CTP-692 was approximately 19 hours which enables once-daily dose administration
4. Accumulation of CTP-692 was minimal to modest following 7 consecutive days of administration
5. Food decreased the rate of absorption (delayed $t_{max}$ and lower $C_{max}$,) but not the extent of absorption (similar AUC under fasted and fed conditions)