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The Pharmacokinetic and Safety Profile of CTP-692 (Deuterated D-serine) in Healthy Volunteers: Phase 1 Program Results

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CTP-692: Potential Adjunctive Treatment for Schizophrenia

- CTP-692: deuterated D-serine
  - NMDA receptor co-agonist
  - Distinct mechanism added to existing standard of care
- Patients with schizophrenia have low levels of D-serine
- Academic studies with D-serine show benefit on negative and positive symptoms of schizophrenia as well as effects on cognitive function
  - Use of D-serine may be limited by renal safety concerns
- Indication: Adjunctive treatment of schizophrenia

CTP-692 Has the Same NMDA Receptor Pharmacology as D-serine

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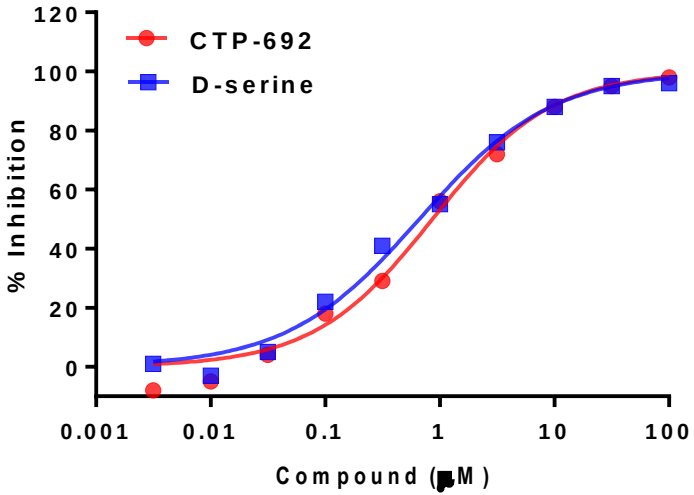
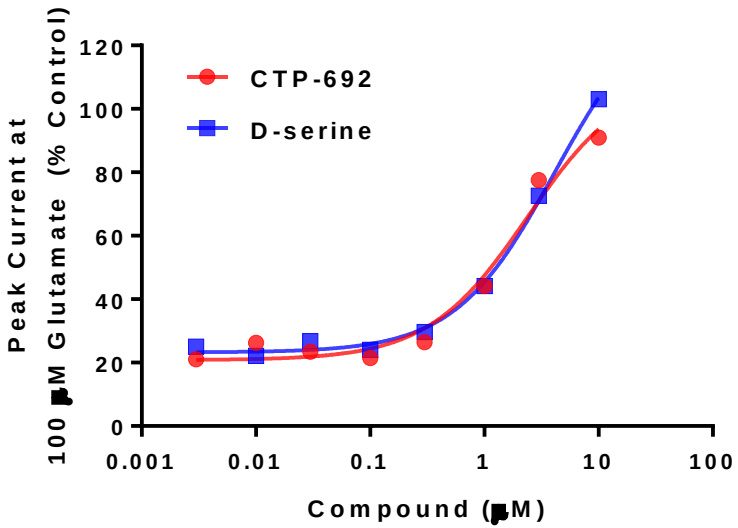
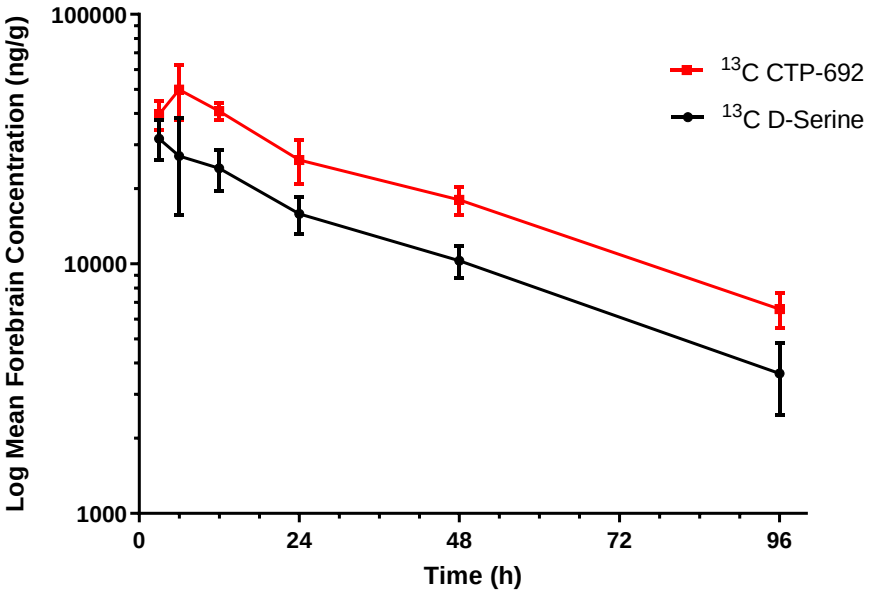
Receptor Binding
CTP-692 binds NMDA receptors the same as D-serine



Receptor Function
CTP-692 activates NMDA receptors the same as D-serine



CTP-692 Has Increased Brain Exposure Compared to D-serine in Nonclinical Evaluation



- CTP-692 concentration is higher in rat forebrain
- CTP-692 exposure in rat forebrain ~2X D-serine exposure

See ASCP 2020 Poster # 38, Brummel CL et al: CTP-692, a Novel Deuterium-Modified D-serine, Produces Higher Brain Exposure in Rats Compared to D-serine

CTP-692: Improved Nonclinical Renal Safety

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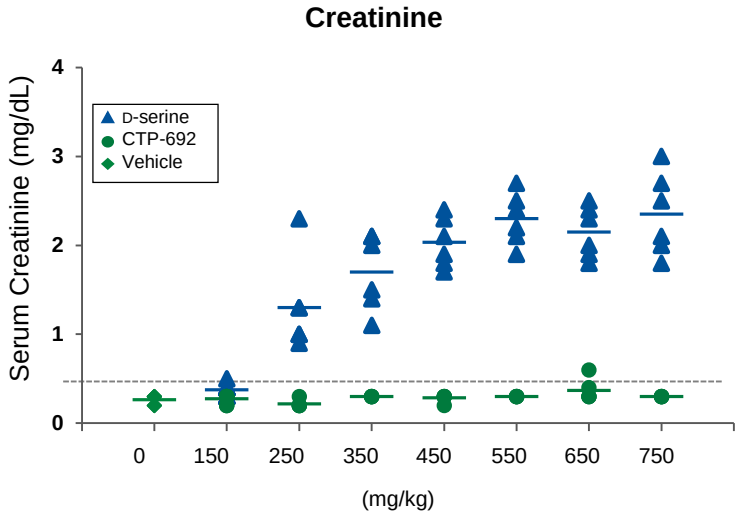

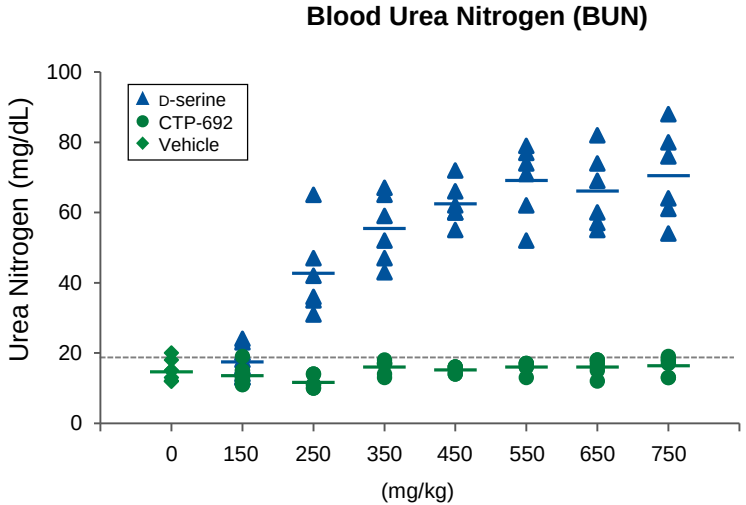

- Significant difference between CTP-692 vs D-serine in rats with respect to markers for nephrotoxicity
  - Levels of creatinine or BUN were relatively stable across all doses in rats treated with CTP-692
  - Abnormally elevated creatinine and BUN were found for all rats receiving D-serine at doses of 250 mg/kg and above
- CTP-692 may represent a reduced risk of nephrotoxicity compared to D-serine

CTP-692 Phase 1 Single- and Multiple-Ascending Dose Trials

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SAD Study Design

Cohort 1 (6 active/2 placebo)	0.5 g CTP-692 or matching placebo
Cohort 2 (8 active/2 placebo)	1 g CTP-692 or matching placebo
Cohort 3 (6 active/2 placebo)	2 g CTP-692 or matching placebo
Cohort 4 (6 active/2 placebo)	3 g CTP-692 or matching placebo
Cohort 5 (6 active/2 placebo)	4 g CTP-692 or matching placebo

MAD Study Design

CTP-692 or placebo administered once-daily for 7 consecutive days

Cohort 1 (8 active/2 placebo)	1 g CTP-692 QD or matching placebo
Cohort 2 (8 active/2 placebo)	2 g CTP-692 QD or matching placebo
Cohort 3 (8 active/2 placebo)	4 g CTP-692 QD or matching placebo

- CTP-692 administered orally as a solution formulation
- Safety and PK assessments
- Exploratory assessment of neurocognitive effects using CogScreen® in both studies

CTP-692 Single-Ascending Dose PK Profile

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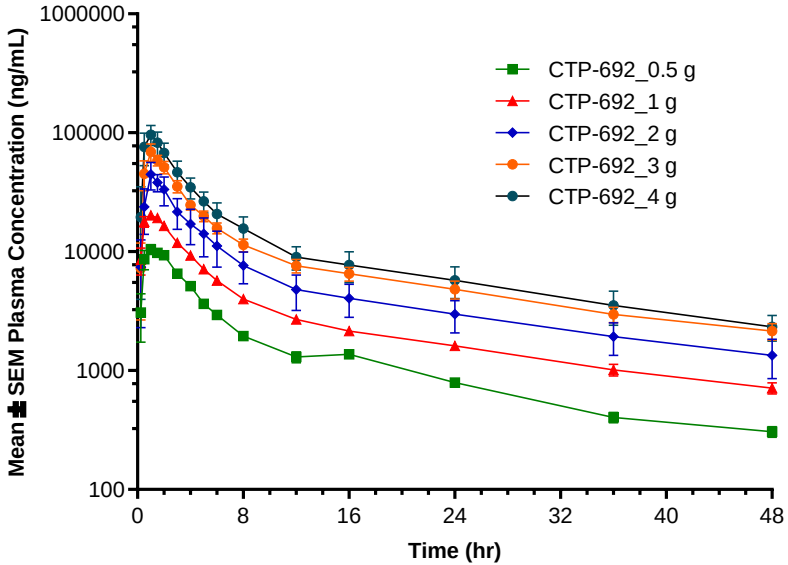

Mean (CV%) PK Parameters

CTP-692 Dose	T_{max}[a] (hr)	C_{max} (μg/mL)	$AUC_{0\text{-}inf}$ (μg*hr/mL)	$T_{1/2}$ (hr)	CL/F (L/hr)
0.5 g (N=6)	1.0 (0.5-1.5)	11.0 (26%)	82.2 (13%)	15.9 (9%)	6.2 (13%)
1 g (N=8)	1.0 (0.5-1.5)	22.3 (21%)	164 (18%)	19.2 (22%)	6.3 (17%)
2 g (N=6)	1.0 (0.5-1.5)	46.3 (20%)	315 (21%)	20.2 (22%)	6.6 (19%)
3 g (N=6)	1.0 (0.5-2.0)	69.1 (40.5%)	489 (27%)	20.6 (9%)	6.6 (31%)
4 g (N=6)	1.0 (0.5-1.0)	96.5 (19%)	618 (21%)	18.4 (15%)	6.7 (20%)

[a] Median (range)

- CTP-692 had a well-defined PK profile with low inter-individual variability
- The CTP-692 dose-exposure relationship was linear
- The terminal $t_{1/2}$ of CTP-692 was approximately 19 hours which enables once-daily dose administration

CTP-692 Multiple-Ascending Dose PK Profile

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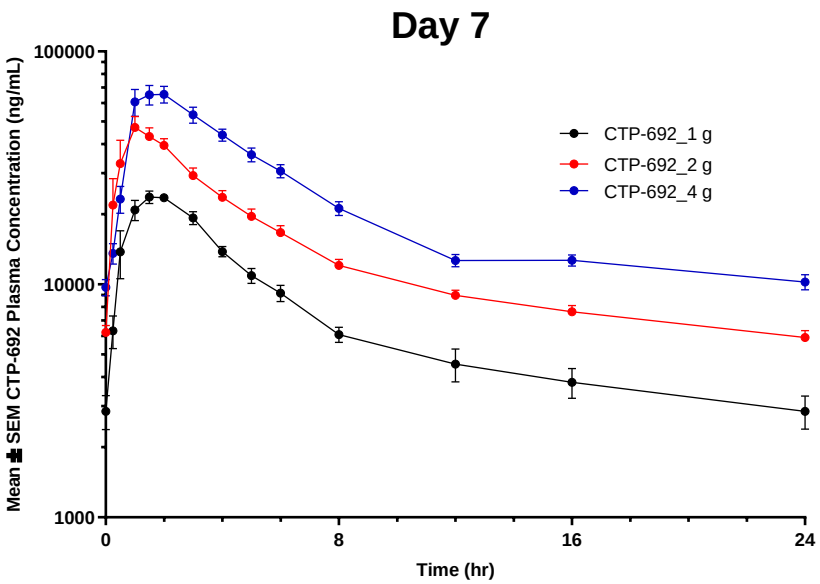

Mean (CV%) PK Parameters

CTP-692 Dose	T_{max}[a] (hr)	C_{max} (µg/mL)	AUC_{tau} (µg*hr/mL)
Day 1			
1 g (N=8)	1.5 (1.0-3.0)	22.2 (14%)	136.4 (14%)
2 g (N=8)	1.0 (1.0-2.0)	47.9 (23%)	258.6 (13%)
4 g (N=8)	1.5 (1.0-2.0)	68.9 (30%)	393.5 (11%)
Day 7			
1 g (N=8)	1.5 (0.5-3.0)	25.3 (12%)	175.3(23%)
2 g (N=8)	1.0 (0.25-2.0)	52.0 (23%)	332.5 (11%)
4 g (N=8)	2.0 (1.0-4.0)	70.8 (26%)	539.1 (14%)

[a] Median (range)

- Steady-state achieved ~ Day 5
- Linear dose-exposure relationship at steady-state
- Accumulation of CTP-692 was minimal to modest following 7 consecutive days of once-daily dose administration

CTP-692 Generally Well Tolerated in SAD and MAD Trials

- All adverse events were mild to moderate and resolved by the end of study
- No dose-related trends in adverse events
- The most common adverse event was headache
- All serum and urine kidney function parameters remained within normal range in both studies

Phase 1 Single-Ascending Dose Trial

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

Phase 1 Multiple-Ascending Dose Trial

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

CTP-692 Phase 1 Results Showed Favorable Safety, Tolerability and Pharmacokinetic Profile

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- Safety assessments in the single- and multiple-ascending dose trials showed CTP-692 was well tolerated over the dose ranges tested
- Key blood and urine markers of kidney function did not indicate any signs of renal impairment
  - Data are consistent with CTP-692 nonclinical findings indicating an improved renal safety profile compared to non-deuterated D-serine
- Exploratory CogScreen included tests of digit symbol substitution (processing speed), previous number recall (working memory), verbal working memory, executive functioning, reaction time, and vigilance
  - Results showed no evidence of adverse effects on neurocognitive functioning at any of the 5 doses
- CTP-692 has a well behaved PK profile with low inter-individual variability
  - Dose-related increases in exposure

CTP-692: Phase 2 Development

- Indication: adjunctive treatment of schizophrenia
- Phase 2 trial initiated December 2019 (ClinicalTrials.gov Identifier: NCT04158687)
  - Approximately 300 patients will be randomized: schizophrenia diagnosis; stable on antipsychotic medication
  - Primary endpoint: change in total Positive and Negative Syndrome Scale (PANSS) score at Week 12 from baseline
  - Secondary endpoints: change in Clinical Global Impression-Severity (CGI-S) and Personal and Social Performance (PSP) scale
  - Dosing: 1, 2 or 4 grams of CTP-692 vs. placebo once-daily