A Phase 1, Single-Center, Open-Label, Single-Dose PK and Safety Study of CSTI-500 in Prader-Willi Syndrome

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Background

CSTI-500 is a first-in-class, oral triple monoamine reuptake inhibitor (TRI) developed to target core symptoms of Prader-Willi Syndrome (PWS), including neurobehavioral dysregulation and hyperphagia. CSTI-500 modulates serotonin, dopamine and norepinephrine levels by simultaneously inhibiting the three respective transporters, SERT, DAT, and NET. The monoaminergic systems are critical to regulating satiety, mood, impulse control and energy balance (Figure 1), but are dysregulated in PWS.[1]

CSTI-500 increases central monoamine levels by blocking reuptake in key brain regions. Clinical research indicates that normalizing these signals - when doses are individually titrated to achieve therapeutic concentrations - can attenuate hyperphagia and improve mood and behavior in individuals with PWS.[2]

CSTI-500 is a uniquely and optimally balanced TRI that has the potential to provide a single-agent solution for PWS's complex neuropsychiatric profile. Learnings from reported studies and off-label clinical practice with other single and dual reuptake inhibitors suggest that PK-guided, personalized dosing will be critical to the success of the treatment. The purpose of this study is to understand the PK of CSTI-500 in individuals with PWS to inform future PK-guided efficacy trials.

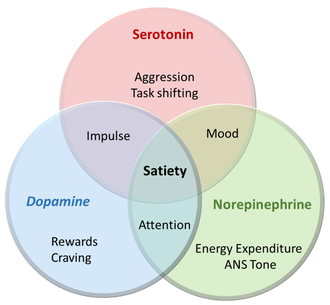


Figure 1. This diagram illustrates key functions regulated by serotonin, dopamine and norepinephrine. CSTI-500, a triple monoamine reuptake inhibitor (TRI), blocks transporters SERT, DAT, & NET to correct the monoamine dysregulation.

***SERT**: Serotonin Transporter;*
***DAT**: Dopamine Transporter;*
***NET**: Norepinephrine Transporter*
***ANS**: Autonomic Nervous System*

CSTI-500 in vitro radioligand binding affinities:
***SERT**: 1.93 ± 0.28 nM*
***DAT**: 22.81 ± 1.95 nM*
***NET**: 33.85 ± 2.82 nM*

Prior Clinical Studies

In two Phase 1 trials (SAD/MAD; N=87 healthy volunteers exposed), CSTI-500 was generally well tolerated. PET imaging study confirmed target engagement in the form of transporter occupancies with a clear PK–PD relationship.[3]

Study Aims

Primary:

- To assess the pharmacokinetics of CSTI-500 in subjects with PWS following a single 10 mg dose.

Secondary:

- To compare CSTI-500 PK values obtained from venous blood draws with those from finger prick samples (Volumetric absorptive microsampling, VAMS) in PWS subjects
- To assess the bioavailability of the new capsule formulation
- To evaluate the safety of a single 10 mg dose of CSTI-500 in PWS subjects

Study Design

Phase 1, open-label, single center (Vanderbilt University Medical Center)

Population: 10 genetically confirmed PWS subjects

- 6 adults (3 male, 3 female); 4 adolescents (1 male, 3 female)

Intervention: Single 10 mg oral dose of CSTI-500, fasted

PK/Safety Assessments:

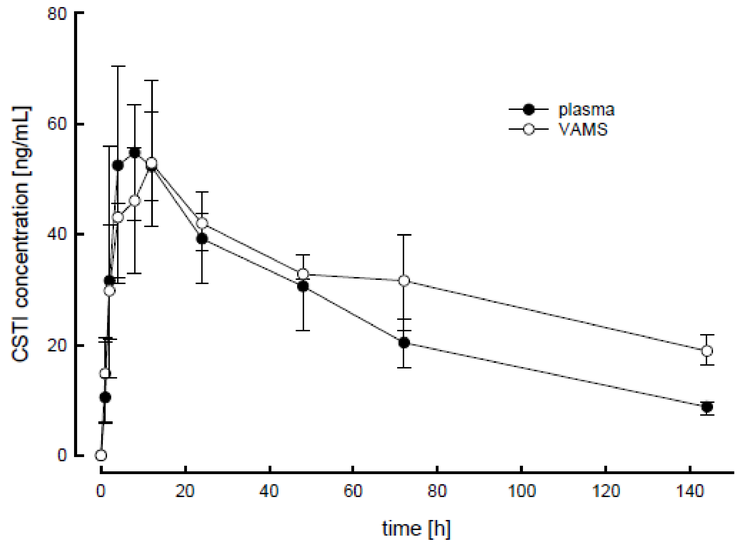
- Safety, blood draws and VAMS at pre-dose, 1, 2, 4, 8, 12, 24, 48, 72, and 144 h
- Safety labs, ECG, vitals at each timepoint
- Follow-up call at 15 ± 3 days after dosing to review AEs, concomitant meds

Results: Pharmacokinetics

1. Plasma vs. VAMS Concentrations

- **0–48 h:** Plasma and VAMS concentrations were comparable through the 48-hour sampling time point
- **48–144 h:** VAMS > Plasma, and this difference was statistically significant at 144 hours.
  - **AUC_{last} ratio (VAMS/Plasma) at 144 h:** 1.39 (p = 0.0006)
  - **AUC_{∞} ratio (VAMS/Plasma):** 1.64 (p = 0.0003)

Figure 2. Mean CSTI-500 concentration–time profiles (log scale) in plasma vs. VAMS (n = 10).



2. Comparison to Healthy Volunteers (HVs)

- The PK of CSTI-500 in PWS patients was comparable to that in healthy volunteers from the previous single ascending dose (SAD) study (CN166001).
- No statistical differences were observed except for a longer Tmax in PWS
- The longer Tmax in PWS indicated a protracted absorption, which is consistent with the capsule formulation used in PWS versus the powder-in-vial formulation used in HVs.

Table 1. Comparison of key plasma PK parameters in the first 24 hours of the current PWS study vs. healthy adult participants in the SAD CN166001 study after a single 10 mg dose.

Data are presented as median (grey) and interquartile ranges (white). Data were compared using an independent two-sided t-test after log-transformation of the data, except T1/2 and Tmax, which were not log-transformed before the t-test. Statistically significant results (p<0.05) are in bold.

Study	$T_{1/2}$	T_{max}	C_{max}	C_{last}	AUC_{last}	AUC_{inf}	$AUC_{0\text{-}24h}$	$AUC_{0\text{-}72h}$	Vz/F	CL/F
	[h]	[h]	[ng/mL	[ng/mL]	[h·ng/mL]	[h·ng/mL]	[h·ng/mL]	[h·ng/mL]	[L]	[L/h]
CN166001	50.1	2.0	66.1	5.74	2982	3374	1059	2184	222.8	2.97
	44.1-55.7	2.0-2.0	62.4-68.3	4.74-8.46	2603-3115	2940-3989	939-1083	1921-2290	192.2-251.7	2.61-3.55
ConSynance CSTI-500-003 (present study)	54.3	6.0	60.7	8.95	3345	4256	991	2418	183.3	2.35
	48.0-59.1	4.0-8.0	53.9-70.2	7.40-9.82	2796-3728	3635-4509	887-1274	2070-2737	163.5-254.9	2.22-2.76
two-tailed t-test (p<)	0.472	**0.010**	0.535	0.257	0.692	0.462	0.841	0.748	0.825	0.462

Results: Safety and Tolerability

- No AEs related to CSTI-500
- 1 mild AE, unrelated to CSTI-500 was reported (mild gastrointestinal disorder)
- Labs/ECG/Vitals: No clinically significant changes
- Conclusion**:** Single 10 mg dose was safe and well tolerated in this PWS study

Table 2. Overview of Adverse Events

Categories	(N = 10)
Any Participant with TEAE	1
Any Participant with Study Drug Related TEAE	0
Any Participant with Severe TEAE	0
Any Participant with Serious TEAE	0
Any Participant with TEAE Leading to Discontinuation	0
Any Participant with TEAE Leading to Death	0

Abbreviations: TEAE = treatment emergent adverse event
Participants who reported more than one event were counted only once.
A TEAE is defined as an AE that occurred from the first dose until the end of Day 8, for each treatment.
Drug-related is any possible, probable, definite, or missing relationship.

Conclusions

1. A single 10 mg oral dose of CSTI-500 was well tolerated in subjects with PWS.
2. The PK profile in PWS subjects was generally similar to that in healthy subjects, with a trend toward delayed absorption.
3. Plasma and finger-prick sampling methods yielded comparable PK results through 48 hours post-dose.
4. Finger-prick concentrations were higher than plasma concentrations at later timepoints (48–144 hours).
5. Interpretation is limited by the single-dose design and lack of steady-state exposure.

Future Plan

A Phase 2a, multiple-dose study in individuals with PWS is planned to evaluate CSTI-500's safety, tolerability, and efficacy on hyperphagia and behavioral symptoms, using personalized, PK-guided dosing.

Acknowledgements

We extend our gratitude to the participants and their families, whose commitment to finding a treatment for PWS made this study possible.

References:

1. *a) Akefeldt et al. (1998); b) Wieting et al. (2023).*
2. *a) Saniona Corp. Presentations 2022 & 2019; b) Appel et al. (2014); c) Deest et al. (2021); d) Meyer et al. (2004)*
3. *Dvorak et al, 2020 PWS Research Symposium, Sept 30-Oct 1, 2020*

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