A Novel Triple Monoamine Reuptake Inhibitor for The Treatment of Rare Obesity Disorders: Pharmacology of CSTI-500 and Phase 1 Clinical Trial Results

FOUNDATION FOR PRADER-WILLI RESEARCH

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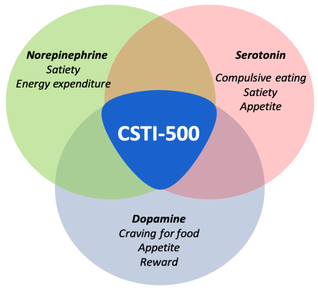
ConSynance THERAPEUTICS

Background

CSTI-500 is a novel, potent and selective triple monoamine reuptake inhibitor (TRI) via blocking serotonin transporter (SERT), dopamine transporter (DAT) and norepinephrine transporter (NET) simultaneously. Serotonin, dopamine and norepinephrine regulate a multitude of behavioral and physiological processes related to eating (Figure 1). CSTI-500 is currently in development for hypothalamic injury-induced obesity and Prader-Willi Syndrome. Our aim is to present the results from preclinical pharmacology and clinical phase I studies.

Figure 1

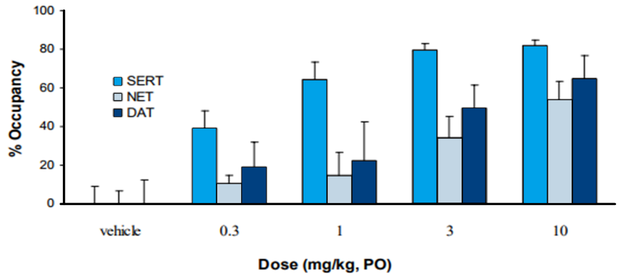


I Preclinical Pharmacology

***In vitro* potency in radioligand binding studies[1]:**
SERT 1.93 ± 0.28nM, NET 33.85 ± 2.82 nM, DAT 22.81 ± 1.95 nM

Brain transporter occupancy in mice determined via *Ex Vivo* binding[2].

Figure 2: SERT, NET and DAT occupancy of CSTI-500 in mouse brain 70 min post dose (n = 4 per dose group, data expressed as mean ± SEM)



II Single Ascending Dose (SAD) study

Design: Double blinded, randomized, placebo-controlled study in healthy males
Dosing groups: 0.5, 2.5, 10, 25, 50, 100, 150 mg (CSTI-500:placebo=6:2)

Pharmacokinetics

- Proportional to CSTI-500 dose - low-moderate inter-subject variability.
- Readily absorbed, median T_{max} ≈ 2 h.
- Mean $T_{1/2}$ ranged from 44-51 h; Clearance = 2.3-3.1 L/h.

Safety and Tolerability

- Safe and well-tolerated up to 100 mg
- Most frequently AEs nausea, dizziness and headache (mild/moderate)
- Episodes of nausea and vomiting determined non tolerated dose of 150 mg

Positron emission tomography (PET) imaging

- PET imaging was conducted before and after a single dose of the maximum tolerated dose of CSTI-500 (100 mg) to enable estimation of SERT and DAT occupancy (Table 1). [3]

Table 1

Time post dose (hours)	SERT occupancy (mean, n=4)	DAT occupancy (mean, n=5)
4-9	72%	36%
24	62%	31%

III Multiple Ascending Dose (MAD) study

Study background

Design
- Double-blinded placebo-controlled study in healthy subjects
- Assessments: safety, tolerability, PK and occupancy

Dosing groups:
- Males: 3, 10, 30, 45, 60 mg/day (CSTI-500:placebo=6:2)
- Females: 45 mg/day (CSTI-500:placebo=6:1)

Dosing regimen:
- 14 days, once daily
- Implementation of titration by administration of 30 mg for the first 3 days and from day 4 to the specified dose (45 and 60 mg)

Pharmacokinetics

- Similar to that in SAD; no evidence of time-dependency
- CSTI-500 is readily absorbed (T_{max} ~ 2 h) and long half-life ($T_{1/2}$ ~50 h)
- Low to moderate inter-subject variability
- Steady state by Day 10 or slightly later due to titration (45-60 mg)

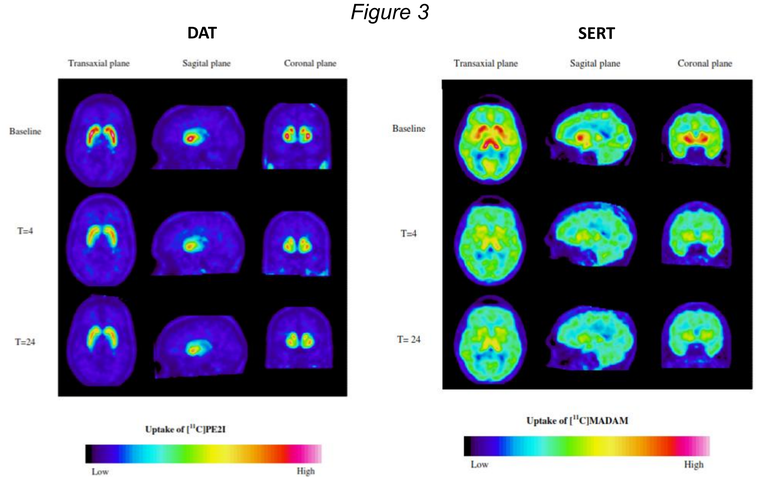
Safety and tolerability

- All doses in males and females tolerated during 14-day treatment period
- Most common AES were headache, nausea, sleep disorder
- Abuse liability potential considered as minimal. No euphoric mood reported.
- Cardiovascular observations:
  - Similar blood pressure in subjects treated with CSTI-500 and placebo
  - CSTI-500 was associated with increased HR upon standing
  - Profile has similarities to DNRIs with less potential to impact BP
  - Possible exacerbation of pre-existing postural orthostatic tachycardia in two young, lean females. Consistent with NRI pharmacology.

PET imaging

Post dosing PET scans were conducted at day 10 (4 h pld) and day 14 (24 h pld)) assuming steady state conditions. For illustrating purposes PET-images are displayed before and after multiple doses of 45 mg CSTI-500 using the specific DAT and SERT tracers ^{11}C-PE2I and ^{11}C-MADAM, respectively.

Figure 3

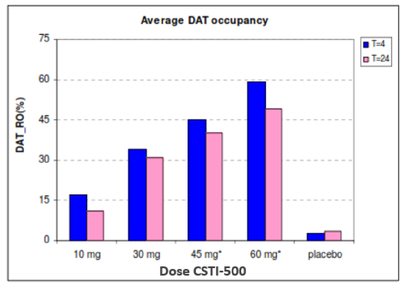


DAT and SERT occupancy

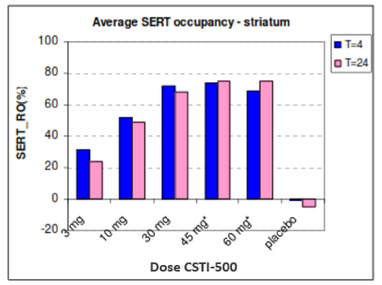
In the PET part of this MAD study only male subjects were considered. Each dose group of 8 subjects was divided in two PET cohorts of 4 subjects with CSTI-500: placebo=3:1. For all doses SERT occupancy was investigated (3-60 mg) whereas DAT occupancy was not investigated for the 3 mg dose group. In total 36 healthy male subjects from MAD groups participated in the PET examinations (SERT, n=20; DAT, n=16). The estimated occupancies were based on a kinetic modelling approach[3] and the results are given in Figure 4.

Figure 4

DAT occupancies (DAT_RO%) at T hours post dose in striatum following multiple doses at SS



SERT occupancies (SERT_RO%) at T hours post dose in striatum following multiple doses at SS



- The obtained SERT occupancy indicates a similar therapeutic SSRI level of serotonin reuptake inhibition for CSTI-500 as reported for established SSRIs.
- The nearly proportional DAT occupancy allows for achieving TRI synergy safely tailored to an individual patient.
- Based on the preclinical profile we expected for NET an occupancy in the same range as for DAT.
- So far CSTI-500 is the only TRI to demonstrate such a profile in human

Weight loss

Substantial weight loss observed over the 14-day treatment period

- Males: ~2.5% loss in 30-60 mg dose groups vs no change in placebo and dose groups below 30 mg
- Females ~4.5% loss in the 45 mg dose group.

Conclusions

- CSTI-500 is a potent, selective and competitive TRI *in vitro* and *in vivo*
- Both PK and occupancy data support once-a-day dosing
- Generally safe and well-tolerated in healthy humans and without abuse liability. AE profile of CSTI-500 is consistent with pharmacology of monoamine inhibition
- PET study demonstrated solid brain target occupancy within the therapeutic ranges of approved SSRI, SNRI, NRI and DNRIs
- A significant weight loss during 14-day treatment opens opportunities for further development as a treatment for rare obesity disorders.

References

1. Liu, S et al. ACS medicinal chemistry letters vol. 5,7 760-5
2. Lengyel, K. et al. Neuropharmacology vol. 55,1 (2008): 63-70.
3. Zheng, M. et al. Psychopharmacology vol. 232,3 (2015): 529-40