A PHASE 3, DOSE-OPTIMIZED, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SINGLE-CENTER, PARALLEL EFFICACY AND SAFETY LABORATORY CLASSROOM STUDY IN ADULTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) USING CTX-1301 (DEXMETHYLPHENIDATE)

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ABSTRACT

Purpose:
To evaluate the safety and efficacy of CTx-1301 in adults with ADHD in a laboratory classroom setting. This study attempted to identify the onset and duration of effect. Effect size was used by determining magnitude of changes in PERMP scores between CTx-1301 and placebo. This could help determine sample sizes of future studies.

Methods:
This is a single-center, dose-optimized, randomized, double-blind, placebo-controlled, laboratory classroom study. Safety and efficacy were assessed using the Permanent Product Measure of Performance (PERMP), Adult ADHD Investigator Symptom Rating Scale (AISRS), Clinical Global Impressions Scale (CGI) and Mini International Neuropsychiatric Interview (MINI) scales*. The study was comprised of a 45-day screening period, 5-week dose-optimization phase (dose range 25mg-50mg/day), 7-day double-blind, randomized, efficacy phase, and a safety follow-up visit.

Results:
Twenty-eight patients were screened, 26 were enrolled and 21 completed the study. 11 subjects received the CTx-1301 and 10 received placebo. Subjects who were randomized to their optimized dose of CTx-1301 showed improvements on the PERMP scores (effect size 0.88 to 2.6; average of 1.79) compared to subjects randomized to placebo. CTx-1301 subjects demonstrated an effect size of 1.41 at 30 minutes and 0.98 at 16 hours; corresponding to onset and duration of effect. During the randomized phase, CGI scale demonstrated a statistically significant change in severity of illness for CTx-1301 (-1.2) vs placebo (0.0), (p <0.001). Treatment emergent adverse events during the randomized period were 9% for CTx-1301 subjects and 30% of subjects randomized to placebo.

Conclusions:
Although this study was not powered for statistical significance, there was clinically meaningful improvement of PERMP scores in subjects who were randomized to CTx-1301, an improvement in the severity of illness and a favorable safety profile compared to placebo.

BACKGROUND

Attention Deficit Hyperactivity Disorder is a common neurodevelopmental disorder impacting 10% of children <18 years and 4.4% of adults in the US. (www.NAMI.org). Current first-line therapies include long-acting stimulant formulations of methylphenidate and amphetamine. Despite several formulations, there is still an issue with crash and rebound scenarios primarily occurring in late afternoon. To address this issue co-prescribing of an immediate release formulation and/or increasing the the daily dose to twice daily are commonly observed with long-acting stimulants. In a study of this dynamic, Brown et al. (2017) found up to 60% of patients are impacted by this booster scenario.! With this dynamic, work research has pointed toward clinical effectiveness of stimulants. A meta-analysis of long-acting stimulants in adults found an average effect size of 0.73 (0.5-0.9). (Faraone, 2010)#
Cingulate Therapeutics developed a tri-modal release of dexmethylphenidate (CTx-1301) seeking to provide rapid onset of action, consistent drug exposure/ effect, and prolonged duration of up to 16 hours.

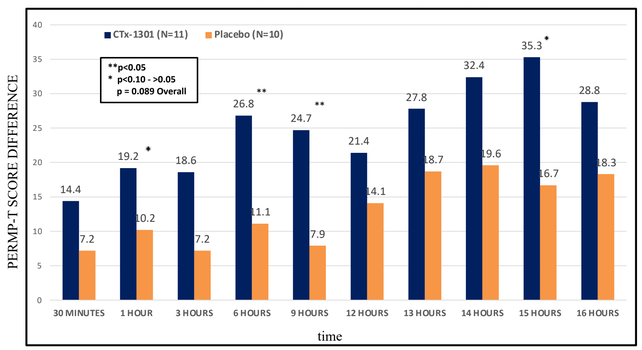
Baseline Patient Population

	Dose Optimization (DOP)%	Randomized Double-Blind Placebo Controlled Period (RPCP)%		
	Total N=26	CTx-1301 N=11	Placebo N=10	Total Treatment Phase N=21
Male	7 (26.9)	1 (9.1)	3 (30.0)	4 (19.0)
Female	19 (73.1)	10 (90.9)	7 (70.0)	17 (81.0)
Age Mean (SD)	34.7 (9.17)	35.0 (10.01)	36.4 (8.60)	35.7 (9.16)
White	20 (76.9)	8 (72.7)	7 (70.0)	15 (71.4)
Black or African	1 (3.8)	1 (9.1)	0	1 (4.8)
American Asian	3 (11.5)	1 (9.1)	2 (20.0)	3 (14.3)
Native Hawaiian or Other Pacific Islander	2 (7.7)	1 (9.1)	1 (10.0)	2 (9.5)

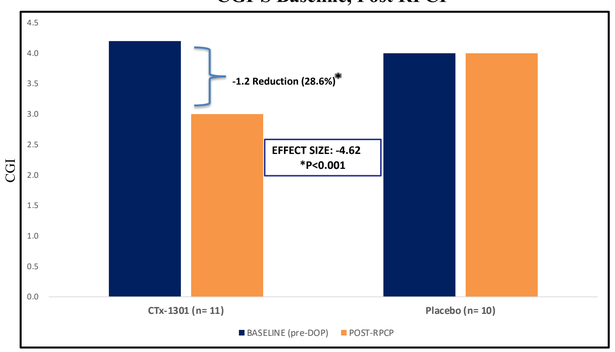
	DOP	RPCP		
	Total N=26	CTx-1301 N=11	Placebo N=10	Total Treatment Phase N=21
ADHD Combined	20	9 (81.8)	7 (70.0)	16 (76.2)
ADHD Inattentive	6	2 (18.2)	3 (30.0)	5 (23.8)
Booster Yes	3	1 (9.1)	1 (10.0)	2 (9.5)
Booster No	12	5 (45.5)	5 (50.0)	10 (47.6)
Missing	11	5 (45.5)	4 (40.0)	9 (42.9)
AISRS Mean (SD)	33.1 (5.18)	32.7 (5.06)	31.9 (3.45)	32.3 (4.28)
CGI Moderate	22 (84.6)	9 (81.8)	10 (100.0)	19 (90.5)
CGI Markedly	4 (15.4)	2 (18.2)	0	2 (9.5)
PERMP-T Mean (SD)	247.0 (65.28)	235.1 (59.97)	260.1 (71.49)	247.0 (65.28)

RESULTS

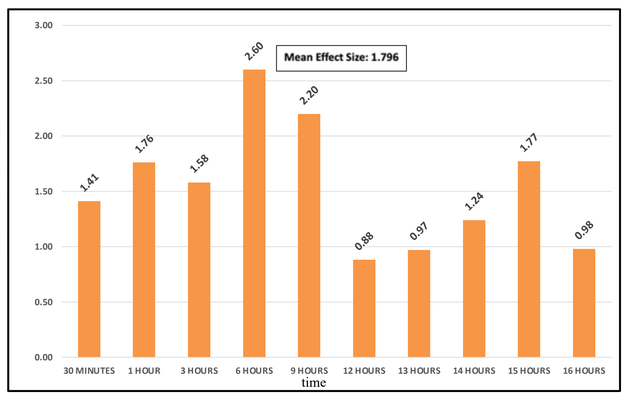
PERMP Score Difference from Baseline



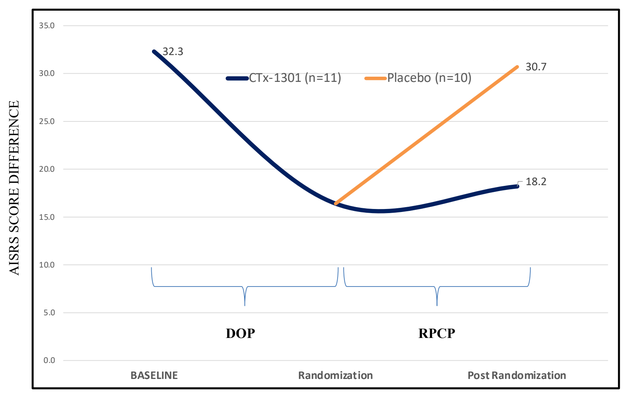
CGI-S Baseline, Post RPCP



PERMP Effect Size: CTx-1301 vs Placebo



AISRS Baseline, Dose Optimization, Post-Placebo adjusted period



Adverse Events

	DOP	RPCP		
	Total N=26	CTx-1301 N=11	Placebo N=10	Total Treatment Phase N=21
Subjects with any treatment-emergent adverse event	25	1	3	4
Dry mouth	15	0	0	0
Anxiety	11	0	0	0
Insomnia	11	0	0	0
Decreased appetite	10	0	0	0
Headache	8	0	1	1
Irritability	7	0	0	0
Nausea	4	0	0	0
Feeling jittery	4	0	0	0
Upper respiratory tract infection	4	0	0	0
Affect lability	3	0	0	0
Gastroenteritis viral	3	0	0	0
Tachycardia	3	0	0	0
Skin and subcutaneous tissue disorders	3	0	0	0
Hyperhidrosis	3	0	0	0
Diarrhoea	2	0	0	0
Bruxism	2	0	0	0
Fatigue	2	0	1	1
Abnormal dreams	0	1*	0	1
Tension headache	0	0	1**	1
Tremor	0	0	1*	1
Gastrooesophageal reflux disease	1	0	1**	1
*Mild. ** Moderate				

SUMMARY AND CONCLUSIONS

1. For CTx-1301 vs placebo, there were trends toward statistical significance for the PERMP ratings over then 16- hour period (p = 0.089). Average Effect Size was 1.79 (0.88-2.60). Treatment Effect Sizes at 30 minutes was 1.41 and at hour 16, effect size was 0.98. As mentioned earlier, in the meta-analysis conducted by Faraone et al. (2010) treatment effects sizes for other long-acting stimulants have ranged from 0.5 to 0.9.
2. CTx-1301 demonstrated a statistically significant (p<0.001) change in CGI-S compared to placebo.
3. CTx-1301 demonstrated a reduction in AISRS scores during the Dose Optimization Period (-16.3).
4. CTx-1301 had one mild treatment emergent adverse event, placebo reported 3 treatment emergent adverse events: 2 moderate and 1 mild. No serious adverse events were reported. No reports of insomnia during the double-blind placebo-controlled period.

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1 Center for Psychiatry & Behavioral Medicine, Las Vegas, NV. 2. Cingulate Therapeutics, Kansas City, KS ! Brown TE: Outside the Box Rethinking ADD/ADHD in Children and Adults. Arlington, VA, American Psychiatric Association, 2017. # Faraone et al. J Clin Psych 2010:71(6) 754-763.

Poster Presented at Psych Congress Nashville, TN | September 7-10, 2023. Poster ID: 1596317 (*PERMP: Permanent Product Measure of Performance. AISRS: Adult ADHD Investigator Symptom Rating Scale. CGI: Clinical Global Impressions Scale. MINI: Mini International Neuropsychiatric Interview) %DOP: Dose Optimization Phase. %RPCP: Randomized Controlled Double Blind Placebo Controlled Phase