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): EFFECT SIZE ASSESSMENT

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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 vs. placebo (-1.1) p <0.001, (effect size -4.62). 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.[1] 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)[#]. Evaluation of individual trials assessing AISRS/ADHD-RS yielded effect size ranges from 0.42-1.11 for long-acting stimulants and 0.28-0.48 for non-stimulants.

Cingulate Therapeutics developed a tri-modal release of dexmethylphenidate (CTx-1301) seeking to provide a rapid onset of action, entire active-day efficacy, and eliminate the need for 'booster' doses.

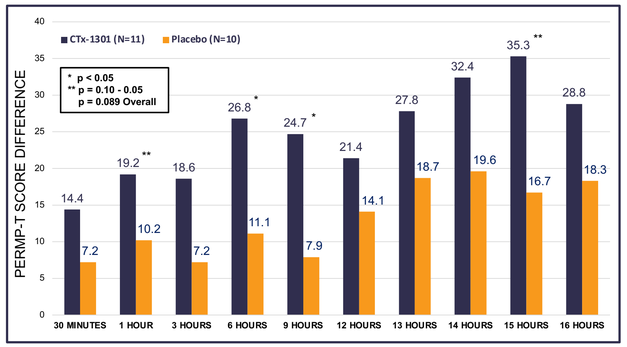
Baseline Patient Population

	Dose Optimization Phase (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)

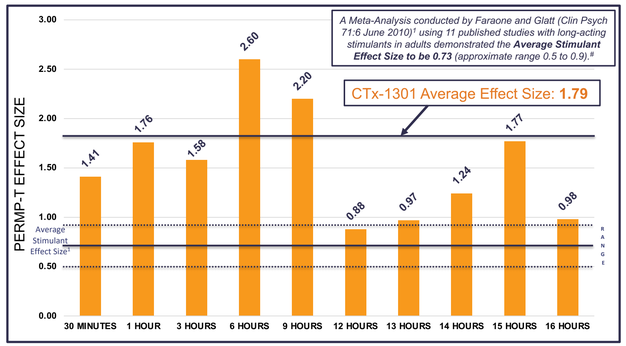
	DOP (%)	RPCP (%)		
	Total N=26	CTx-1301 N=11	Placebo N=10	Total Treatment Phase N=21
ADHD Combined	20	9 (81.8)	7 (70.0)	16 (76.2)
ADHD Inattentive	6	2 (18.2)	3 (30.0)	5 (23.8)
Booster Yes	3	1 (9.1)	1 (10.0)	2 (9.5)
Booster No	12	5 (45.5)	5 (50.0)	10 (47.6)
Missing	11	5 (45.5)	4 (40.0)	9 (42.9)
AISRS 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)

RESULTS

PERMP Score Difference from Baseline



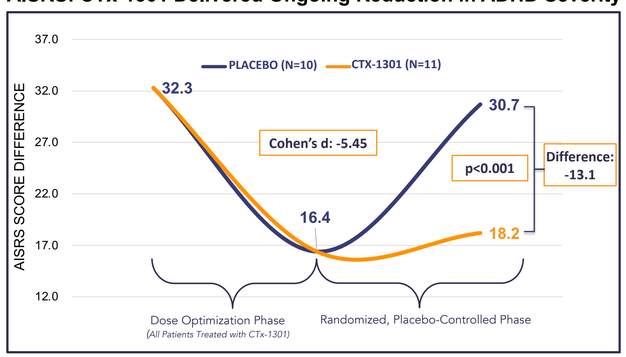
PERMP Effect Size: CTx-1301 vs. Placebo



ADHD Effect Size: Independent Trials*

ADHD Products & Candidate	Peak Effect Size	P-value	Percentiles[#] (Cohen's d)
CTx-1301***	1.79 @ 1 week**[A]	<0.001	95 - 96%
Concerta ®[1*]	0.42 @ 6 weeks**[B]	<0.001	66 - 69%
Vyvanse ®[2*]	0.94 @ 10 weeks**[B]	<0.001	82 - 84%
Focalin XR ®[3*]	0.54 @ 6 weeks**[B]	<0.001	69 - 73%
Azstarys ®[4*]	0.49 @ 4 weeks**[C]	0.003	66 - 69%
Adderall ® XR[5*]	0.80 @ 4 weeks**[B]	<0.001	79%
Mydayis ® XR[6*]	1.11 @ 4 weeks**[B]	<0.001	84 - 88%
Non-Stimulants****(7*,8*)	0.28 - 0.48**[B]	0.004 - 0.012	54 - 69%

AISRS: CTx-1301 Delivered Ongoing Reduction in ADHD Severity



* results, calculations, and data on file Cingulate Inc.
^ PERMP, **[B] ADHD-RS, **[C] WREMB-R scales * CTx-1301 is currently in Phase 3 of clinical development and not an approved product **** Strattera®.[7*] (0.48 at 6 month; p≤0.004; ~69%) and Qelbree® [8](0.28; 0.312 at 6 weeks; p=0.004; ~54%)
[1*] Goodman DW et al. J Clin Psychiatry. 2017 Jan;78(1):105-114. 2*Adler LA, et al. BMC Psychiatry. 2013 Oct 9;13:253. 3*Adler, L. A.et al. J Atten Dis, 2009 12(5), 449-459. 4*Kollins Data from published clinical trial SH et al. J Child Adolesc Psychopharmacol. 2021 Nov;31(9):597-609.
5*Weisler RH et al. CNS Spectr. 2006 Aug;11(8):625-39. 2009. 6*Weisler RH et al. CNS Drugs. 2017 Aug;31(8):685-697. 7*Wietecha LA, et al. CNS Neurosci Ther. 2016 Jul;22(7):546-57. 8*Nasser A, et al. CNS Drugs. 2022 Aug;36(8):897-915.

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
Gastroesophageal reflux disease	1	0	1**	1
*Mild, ** Moderate				

SUMMARY and CONCLUSIONS

1. CTx-1301 demonstrated an Average Effect Size of 1.79 (0.88-2.60). Treatment Effect Sizes at 30 minutes was 1.41 and at hour 16 was 0.98. Versus placebo, there were trends toward statistical significance for the PERMP ratings over the analysis period (p=0.089). 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 28% statistically significant (p<0.001) change in CGI-S compared to placebo.
3. Dose Optimization: 25 mg (38%); 37.5mg (57%); 50mg (5%).
4. AISRS severity score decrease of -16.3 during the DOP.
5. CTx-1301 maintained AISRS severity score decreases and a difference of -13.1 (p<0.001) compared to placebo during the RPCP, Cohen's d Effect Size: -5.45.
6. CTx-1301 had one mild treatment emergent adverse event, placebo reported 3 treatment emergent adverse events, all moderate or mild.

Acknowledgements

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CINGULATE®

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 American Professional Society for ADHD and Related Disorders, January 20, 2024. Poster ID: S18 | **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