Comparative Bioavailability and Safety of a Novel Trimodal Dexmethylphenidate Tablet in ADHD Patients

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ABSTRACT

Objectives: The primary objectives of this study were to compare the bioavailability of two dexmethylphenidate formulations, CTx-1301 (trimodal tablet) vs Focalin®XR (biphasic capsule), and to demonstrate dose proportionality of the CTx-1301. Secondary objectives were to characterize the pharmacokinetics and evaluate safety.

Methods: 45 adult ADHD subjects were randomized to receive single doses of four different d-MPH dosage forms: Focalin XR 5-mg, Focalin XR 40-mg, CTx-1301 6.25-mg, and CTx-1301 50-mg. 22 serial blood samples were obtained over each 28-hour treatment period; plasma profiles were evaluated using a validated bioanalytical method. Statistical results were based on 39 subjects completing all four treatments.

Results: Data confirmed that CTx-1301 exhibited similar systemic d-MPH exposure to Focalin XR over the first 8 hrs. after administration. In addition, CTx-1301 plasma concentrations at 15-16 hrs. were similar to Focalin XR at 12 hrs., thereby demonstrating the potential for an extended duration of action, up to 16 hrs. CTx-1301 also demonstrated a statistically significant higher concentration ($p<0.05$) vs Focalin XR from 9 to 16 hours in both low and high doses. Based on the concentrations observed in the study, CTx-1301 is expected to have a similar onset of action (30 minutes) as Focalin XR. The geometric mean Cmax was 3.07 ng/mL vs 2.82 ng/mL and 23.1 ng/mL vs 24.3 ng/mL for Focalin XR and CTx-1301, low and high doses respectively. Tmax was similar in all treatments (~6 hrs). CTx-1301 ADHD patients experienced a 28.6% reduction in TEAE's vs Focalin XR.

Conclusion: CTx-1301 tablets demonstrated a trimodal pharmacokinetic profile characteristic of fast onset of action, entire active-day duration, and potential to minimize crash and rebound. Phase 3 Trials will be conducted to prospectively evaluate efficacy including onset, duration, safety, and additional pharmacodynamic benefits.

Clinical Trial Information: NCT04138498

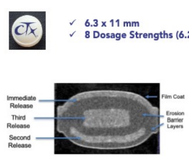
BACKGROUND

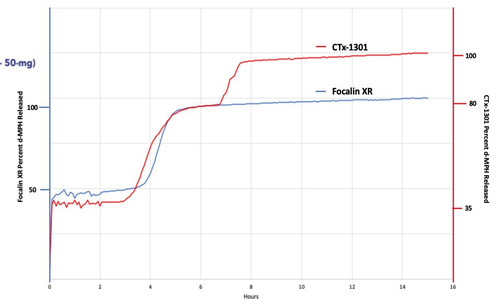
Cingulate™ is achieving optimal once-daily dosing using the company's innovative, proprietary, Precision Timed Release™ (PTR®) drug delivery platform technology which incorporates a patented Erosion Barrier Layer (EBL) providing control of drug release at precise, predefined times. It comprises an immediate-release layer, a delayed extended-release layer, and a final immediate release core. This formulation is designed to provide a fast onset, therapeutically active levels of dMPH lasting 14-16 hours, and eliminate the need for booster dosing.

CTx-1301 has been designed to deliver 25% more d-MPH versus Focalin XR. Cingulate's tri-modal tablet delivers a precisely timed, unique ratio, and style of drug delivery as opposed to the 50%/50% bi-phasic profile with drug release at time 0 and 4 hours. CTx-1301 delivers 35% of the total daily dose at time 0 in an immediate-release formulation, 45% at 3 hours post dose in a sustained-release over 90 minutes, with a built-in-booster of 20% immediate-release at 7 hours post dose.

A comparative in-vitro dissolution study was performed between CTx-1301 25-mg tablets and Focalin XR 20-mg capsules. The dissolution test was conducted in two phases: an acidic solution for 2 hours and a pH neutral phase for the remainder of the 15- hour run.

- ✓ 6.3 x 11 mm
- ✓ 8 Dosage Strengths (6.25 – 50-mg)





SUMMARY

CTx-1301 Demonstrated Plasma Levels at 15-16 hours versus Focalin XR at 12 hours

- ✓ CTx-1301 blood levels demonstrate the potential for a duration of action for the entire active-day, up to 16 hours
- ✓ CTx-1301 performed as designed, with its precise 20% 'built-in-booster'
- ✓ Phase 3 Trials designed to confirm expected duration and additional potential benefits

CTx-1301 Demonstrated Plasma Levels Equal to Focalin XR at 30 Minutes

- ✓ CTx-1301 demonstrates rapid and overlapping blood levels of Focalin XR indicative of a 30-minute onset of action
- ✓ Phase 3 Trials designed to confirm expected 30-minute onset of action

CTx-1301 Demonstrated its Controlled Descent of Plasma Levels versus Focalin XR

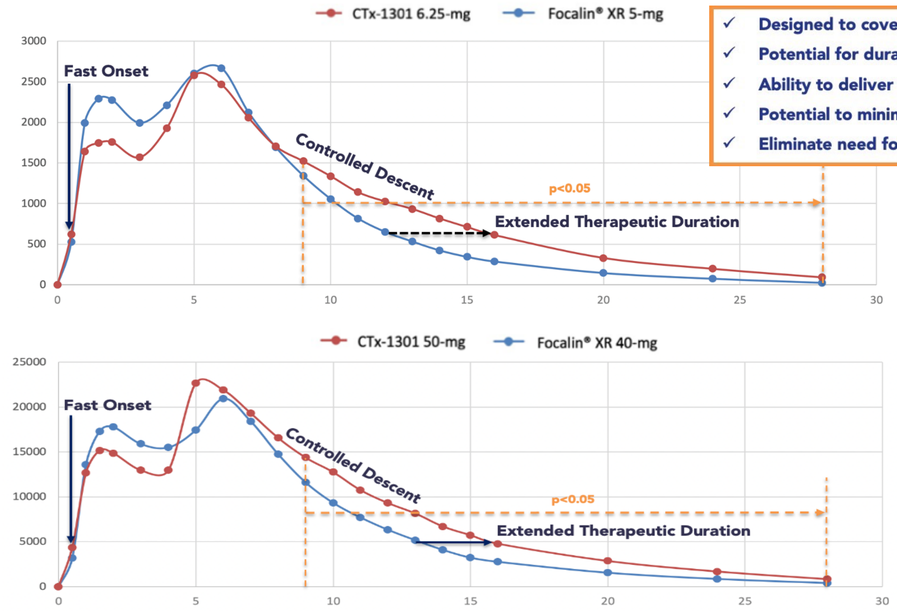
- ✓ CTx-1301's precise 20% 3rd delivery stopped the mid-afternoon plummeting of blood levels, controlling the decline until early evening
- ✓ Phase 3 Trials designed to further investigate the potential benefits of this controlled release to prevent 'wear-off', 'crash/rebound', and eliminate the need for a 'booster or recovery' dose

CTx-1301 Demonstrated Significantly Lower Treatment Emergent Adverse Events

- ✓ ADHD patients received 25% more medication via the PTR™ Platform in a precisely timed, unique ratio
- ✓ CTx-1301 patients experienced a 28.6% reduction of TEAE's related to study drug versus Focalin XR (14.3% difference)

RESULTS

CTx-1301 Phase 1/2 Study Results



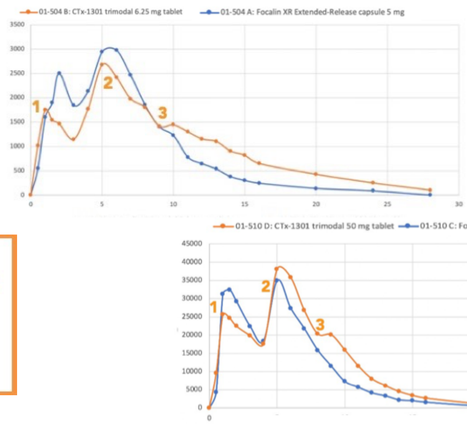
- ✓ Designed to cover the "Entire Active Day"
- ✓ Potential for duration of action up to 16 hours
- ✓ Ability to deliver fast onset of action
- ✓ Potential to minimize 'crash/rebound' effect
- ✓ Eliminate need for "booster" dose

CTx-1301 Demonstrated Significantly Lower TEAE's

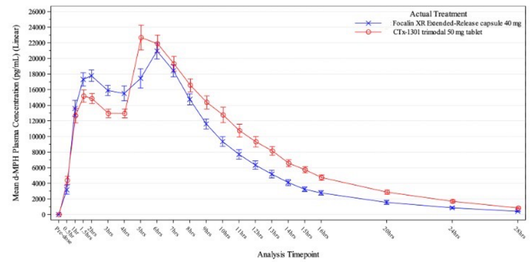
Category	Focalin XR 5-mg Treatment A (N=41)	CTx-1301 6.25-mg Treatment B (N=39)	Focalin XR 40-mg Treatment C (N=43)	CTx-1301 50-mg Treatment D (N=42)	All CTx-1301 (N=42)	All Focalin XR™ (N=44)
All Periods	41	39	43	42	42	44
Subjects with at least one Treatment Emergent Adverse Event (TEAE)	7 (17.1%)	4 (10.3%)	22 (51.2%)	14 (33.3%)	17 (40.5%)	25 (56.8%)
Mild	7 (17.1%)	4 (10.3%)	20 (46.5%)	14 (33.3%)	17 (40.5%)	23 (52.3%)
Moderate	0	0	2 (4.7%)	0	0	2 (4.5%)
Severe	0	0	0	0	0	0
TEAE Related to Study Drug	5 (12.2%)	3 (7.7%)	20 (46.5%)	13 (31.0%)	15 (35.7%)	22 (50.0%)
TEAE Related to Procedure	0	0	1 (2.3%)	0	0	1 (2.3%)
Serious Adverse Event (SAE)	0	0	0	0	0	0
SAE Related to Study Drug	0	0	0	0	0	0
SAE Related to Procedure	0	0	0	0	0	0
Adverse Event Leading to Study or Drug Withdrawal	1 (2.4%)	0	1 (2.3%)	0	0	2 (4.5%)
Adverse Event Leading to Death	0	0	0	0	0	0

Source: CSR CTx-1301-001 Listing 16.2.7.1

At the Individual Patient Level, Tri-modal Delivery is Clear



PTR Technology Delivers Minimal Intersubject Variability



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CINGULATE™ THERAPEUTICS

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