Pharmacoscintigraphic and Pharmacokinetic Analysis of CTx-1301, a Novel Tri-modal Oral Formulation for Release of Dexmethylphenidate in Healthy Adults

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ABSTRACT

Background: CTx -1301 is a dexmethylphenidate (d-MPH) tri-modal tablet formulation comprised of an immediate release layer, a delayed extended-release layer, and a final immediate-release core designed to provide a fast onset, and ultimately therapeutically active levels with d-MPH lasting 14-16 hours. Finally, designing a preparation with a controlled descent of d-MPH was envisioned to minimize the rebound effect and maintain favorable tolerability. The primary focus of the presentation is to describe how the third delayed core performed in terms of where it is delivered in the gut, and how successfully the delivery mechanism achieved the controlled descent.

Methods: A randomized, three-arm, open-label crossover study was performed in 15 healthy volunteers (mean age = 25 years; wt. = 77kg) to establish the PK profile of a novel dexmethylphenidate (d-MPH) modified-release tablet (CTx-1301) using pharmacoscintigraphic methods. Each volunteer underwent three treatment arms receiving a bi-phasic extended-release d-MPH 10mg (Focalin XR®) (Treatment A), and CTx-1301 12.5mg tablets (Treatment B contained a radiolabeled second d-MPH layer, and Treatment C contained a radiolabeled third d-MPH layer). Serial blood samples were taken over a 24-hour period after dosing and plasma concentrations of d-MPH were analyzed for all three groups to determine relevant pharmacokinetic parameters including initial and subsequent C_{max} and T_{max}, as well as AUC $_{(0\text{-}8h)}$, AUC $_{(8\text{-}24h)}$, and AUC$_{(0\text{-}inf)}$. Scintigraphic methods were used to visualize timing and location of release of radiolabeled d-MPH layers from CTx-1301 tablets.

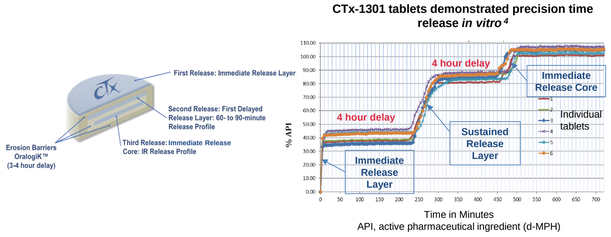
Results: The two CTx-1301 treatment arms demonstrated initial $T_{max\ (0\text{-}4h)}$ of 1.6 hrs and 1.9 hrs versus 2.3 hrs for Focalin XR® and initial $C_{max\ (0\text{-}4h)}$ (4.9 and 5.3 vs 5.9ng.ml^{-1}). The terminal half-life was extended by more than an hour in the CTX-1301 treatments (4.5 and 4.3 hours) versus Focalin XR® (3.0 hours). Scintigraphic measurements determined mean time of release of the CTx-1301 second layer to be 4.7 hr., and the third layer (core) to be 10.3 hr. There was a statistically significant (p<0.005) difference between mean AUC$_{(8\text{-}24h)}$ between CTx-1301 B and C (29.2 & 31.6 hr·ng/ml) and Focalin XR® (17.1 hr·ng/ml). Onset of release of the second CTx-1301 layer was visualized in the small intestine (N=8), caecum (N=3), and ascending colon (N=4), while onset of release of the third layer was visualized in the small intestine (N=1), caecum (N=2), ascending colon (N=4), transverse colon (N=7), and splenic flexure (N=1). No serious adverse events were reported following any treatment.

Conclusion: Mean initial C_{max} and T_{max} values were comparable between the three treatment arms. Second and third delayed-release layers of CTx-1301 were delivered as designed, maintaining blood levels of d-MPH longer than Focalin XR® resulting in a slower descent of d-MPH. Future investigations will include classroom studies to link the pharmacokinetics and clinical efficacy of CTx-1301, including the rebound effect.

BACKGROUND

- Most long-acting stimulant products currently on the market do not remain effective for more than 12 hours after administration, and many patients do not experience clinical efficacy beyond 6-8 hours[1]. It is estimated through clinical observation that this results in approximately 50-60% of college students and adults having to take a third IR dose in the evening, which can lead to unfavorable side effects such as loss of appetite (for dinner) and insomnia[2].
- As blood levels drop precipitously during the latter portions of the day, some patients may also experience a rebound effect, which often manifests in AEs such as irritability, mood changes and worsening of clinical presentations. Commonly known as the "afternoon crash", these undesirable effects are the result of a rapid reduction in plasma levels of dexmethylphenidate in school age children approximately 7-8 hours post-administration, interfering with the end of the school day, after-school activities, and completion of homework[3].
- CTx -1301 is a novel tri-modal dexmethylphenidate (d-MPH) tablet formulation, developed in conjunction with BDD Pharma utilizing proprietary OralogiK® delayed release technology. It comprises an immediate release layer, a delayed extended-release layer, and a final immediate-release core. This is designed to provide a fast onset, and ultimately therapeutically active levels of d-MPH lasting 14-16 hours.
- The preparation is designed to extend duration, provide a controlled descent of d-MPH to minimize the rebound effect, and maintain favorable tolerability.

CTx-1301 tablets demonstrated precision time release *in vitro*[4]



API, active pharmaceutical ingredient (d-MPH)

- In this presentation, we describe how the third delayed dose from the core performed in terms of where it is delivered in the gut, and how this precision timed release technology achieves a controlled descent. Additional results have been previously presented[5]

METHODS

- A randomized, three-arm, open-label crossover study was performed in 15 healthy male volunteers

Treatment

- Single dose of each treatment under fasting conditions with dosing separated by a minimum of 7 days
- **Treatment A**: 10-mg d-MPH commercially obtained Focalin XR® capsules (not radiolabeled)
- **Treatments B and C**: CTx-1301 12.5-mg d-MPH tablets. Treatment B radiolabeled second release; Treatment C radiolabeled third release

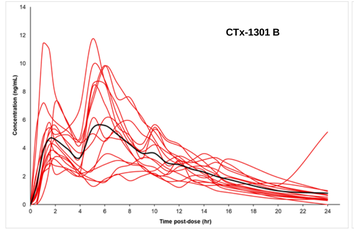
Analysis

- Pharmacokinetics (PK)
  - Blood sampling (21 over 24 hours) was carried out at defined intervals and dose corrected PK parameters were compared across all formulations
  - Maximum Concentration (C_{max}), time of maximum concentration (T_{max}), AUC $_{(0\text{-}8h)}$, AUC $_{(8\text{-}24h)}$, and AUC$_{(0\text{-}inf)}$, and half life ($T_{1/2}$)
- Scintigraphy
  - CTx-1301 radiolabelled (4 MBq technetium-99m) to visualize site and time of *in vivo* release (second or third release layers)
  - Times and sites of visualization of onset and complete release of radiolabel.
  - Gastrointestinal transit parameters – gastric emptying time and colon arrival time of radiolabel, where applicable.
- Safety
  - The assessment of tolerability is based on adverse events collected throughout the study following dosing with the study products.

RESULTS

Figure 1a. Mean d-MPH drug plasma profile for Focalin XR® capsules vs CTx-1301 tablets

Figure 1b. d-MPH plasma profiles for CTx-1301 tablets (Treatments B and C)



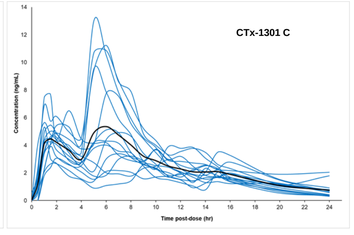


Figure 1c. d-MPH plasma profiles for Focalin XR® (Treatment A)

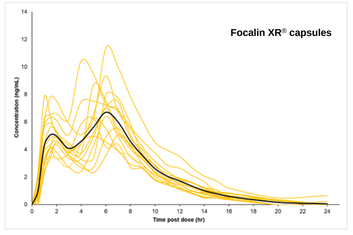


Table 1. Comparison of Mean d-MPH Pharmacokinetic plasma profiles

	CTx-1301		Focalin® XR
	B	C	
Dose (mg)	12.5	12.5	10.0
AUC 0-8h (ng x h/ml)	31.8	33.8	38.3
AUC 8- 24h (ng x h/ml)	29.2†	31.6†	17.1
AUC 0-Inf (ng x h/ml)	51.7* (90%)	54.2* (95%)	57.0
Cmax 0-4h (ng/ml)	4.9 (91%)	5.2 (96%)	5.4
Tmax (hrs.)	1.6	1.9	2.3
Half life (hrs.)	4.5	4.3	3.0

*Normalized AUC to the dose of Focalin® XR; ( ) Value as a % relative to Focalin ® XR
†p<0.05 compare to Focalin® XR

Pharmacoscintigraphic results:

- Mean onset of radiolabel release of the third d-MPH release was at 10.3 ± 1.7 hours; corresponds with the higher d-MPH plasma level AUC$_{(8-24)}$ hours
- Mean onset of radiolabel release for the second d-MPH release was at 4.7 ± 1.3 hours; corresponds with Tmax$_{(4\text{-}8)}$ (5.8 ± 1.2 hr) for the second d-MPH plasma peak

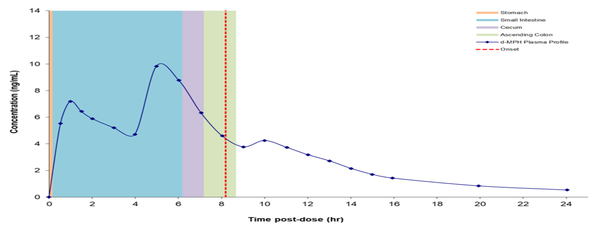
Table 2. Final immediate release Core for individual patients

Location in Gut and Onset time in hours				
Caecum	Ascending Colon	Transverse Colon	Sigmoid Flexure	Small Intestine
2 (10.2 hrs)	4 (9.6 hrs)	7 (10.6 hrs)	1 (12.2 hrs)	1 (9.2hrs)

*values in () are the average

Figure 2. Example of Single Patient Composite profile with radiolabeled release from core

Treatment C, *Single Subject YY* 12.5-mg CTx-1301
d-MPH drug plasma profile with identification of the time and site of radiolabel release from the core



- **Safety** – no major adverse events report and only minor or moderate adverse events consistent with d-MPH use were reported

CONCLUSIONS

- CTx-1301 demonstrated statically significant higher plasma levels compared to Focalin ® XR as demonstrated in AUC $_{(8\text{-}24)}$ due to the third d-MPH release.
- Mean initial C_{max} and T_{max} values were similar between the three treatment arms.
- CTx-1301 tablets second release was similar to d-MPH Focalin XR®
- CTx-1301 novel tri-modal tablets delivered d-MPH as designed, maintaining blood levels longer than Focalin ® XR resulting in a slower descent of d-MPH and offers a potentially new treatment option for ADHD patients
- Future investigations will include classroom studies to link the pharmacokinetics and clinical efficacy of CTx-1301 tri-modal tablets, including the rebound effect.

REFERENCES

1. Silva RR *et al. J Am Acad Child Adolesc Psychiatry* 2008;47(2):199-208.
2. Brown TE *et al. Psychopharmacol Bull* 2017;47(4):18-28.
3. Carson and Kelly *J Child Adolesc Psychopharmacol* 2003;13(2):137-42.
4. Data on File. Cingulate Therapeutics.
5. Abele et al. AAPS Annual meeting, San Diego 2017. Abstract W3099

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