

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

Raul R. Silva¹, MD; Matt Brams¹, MD, Arthur Straughn¹, PharmD; Shane J. Schaffer¹, PharmD; Stephen Abele¹, BS; Howard N.E. Stevens², PhD; Laura Gow², B.Sc; Neil Masson³, MD

¹Cingulate Therapeutics, 1901 W. 47th Place, Kansas City, KS 66205, USA; ²BDD Pharma, 84 Castle Street, Glasgow G4 0SF, UK; ³Stobhill Hospital, Glasgow Scotland, UK

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 h. 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.

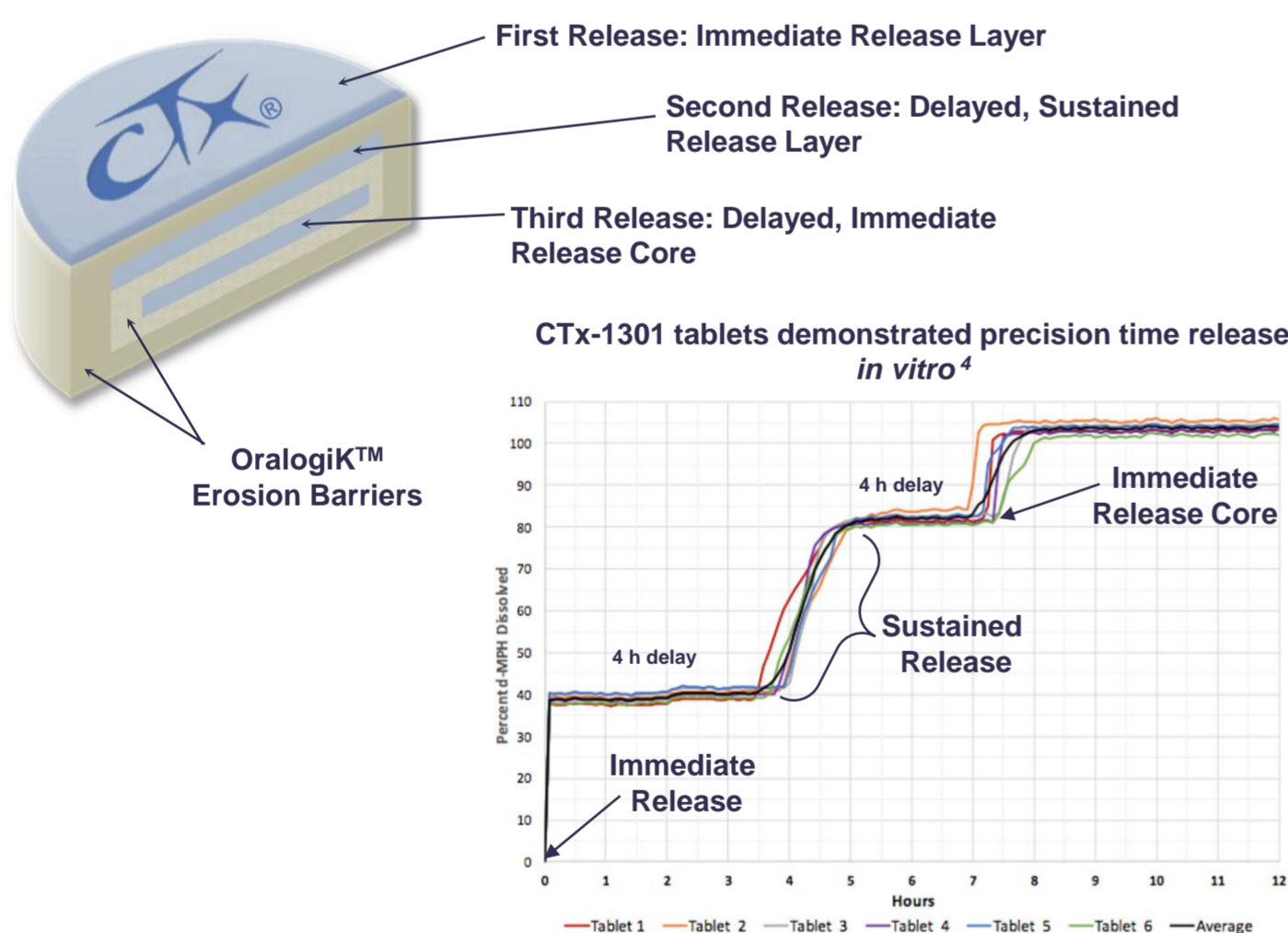
Methods: A randomized, three-arm, open-label crossover study was performed in 15 healthy volunteers (mean age = 25 years; weight = 77 kg) to establish the PK profile of a novel d-MPH modified-release tablet (CTx-1301) using pharmacoscintigraphic methods. Each volunteer underwent three treatment arms receiving a bi-phasic extended-release d-MPH 10 mg (Focalin[®] XR) (Treatment A), and CTx-1301 12.5 mg 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-h 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_(0-8h), AUC_(8-24h), and AUC_(0-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 (0-4h)} of 1.6 h and 1.9 h versus 2.3 h for Focalin[®] XR and initial C_{max (0-4h)} (4.9 and 5.3 vs 5.9 ng/ml⁻¹). The terminal half-life was extended by more than an hour in the CTx-1301 treatments (4.5 and 4.3 h) versus Focalin[®] XR (3.0 h). Scintigraphic measurements determined mean time of release of the CTx-1301 second layer to be 4.7 h, and the third layer (core) to be 10.3 h. There was a statistically significant (p<0.005) difference between mean AUC_(8-24h) between CTx-1301 B and C (29.2 & 31.6 h-ng/ml) and Focalin XR[®] (17.1 h-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 8-12 h after administration, and many patients do not experience clinical efficacy beyond 6-8 h¹. 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 insomnia².
- As blood levels drop precipitously during the latter portions of the day, some patients may also experience a rebound effect, which often manifests in adverse events 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 d-MPH in school age children approximately 7-8 h post-administration, interfering with the end of the school day, after-school activities, and completion of homework³.
- CTx-1301 is a novel tri-modal d-MPH tablet formulation, developed in conjunction with BDD Pharma utilizing proprietary Oralogik[®] delayed release technology. It comprises an immediate release layer, a delayed sustained-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 up to 16 h.
- The preparation is designed to extend duration, provide a controlled descent of d-MPH to minimize the rebound effect, and maintain favorable tolerability.



- 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 presented⁵.

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 h) 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_(0-8h), AUC_(8-24h), and AUC_(0-inf), and half life (T_{1/2})
 - Scintigraphy
 - CTx-1301 radiolabeled (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

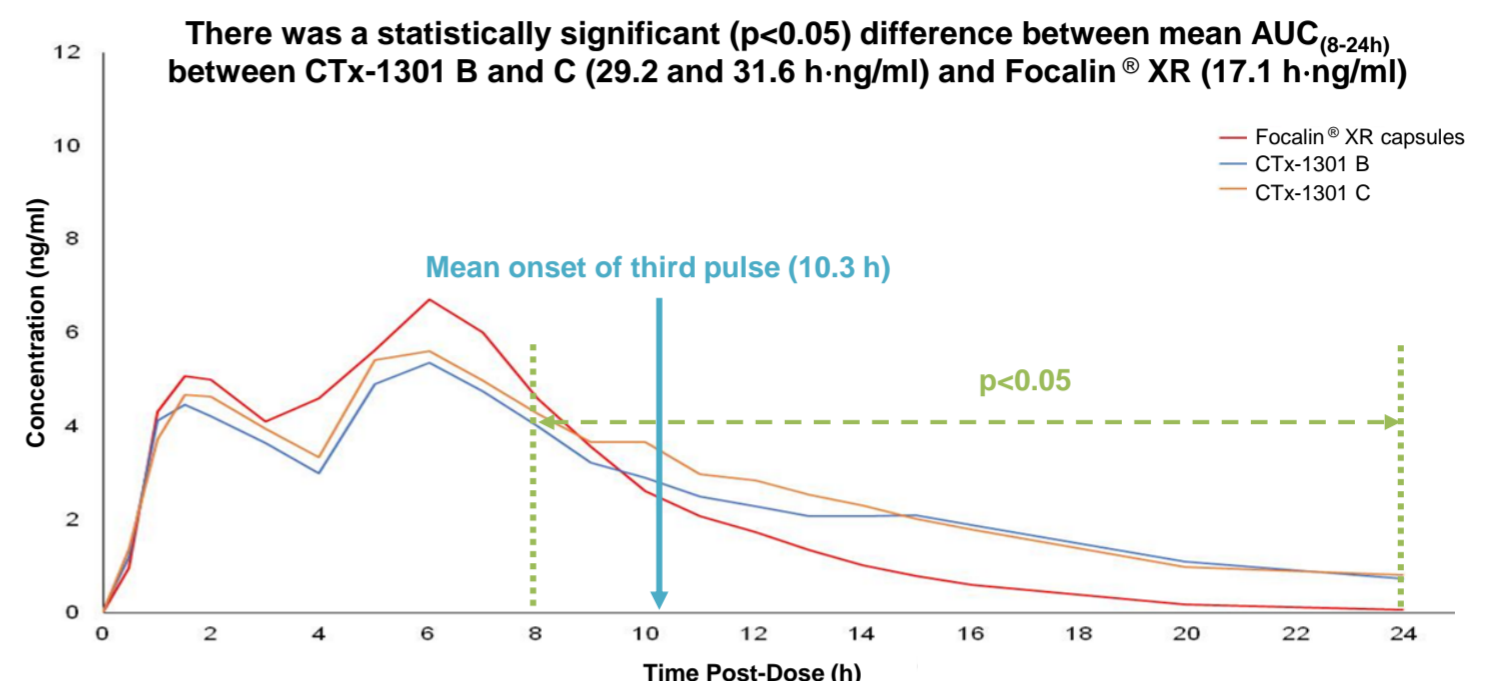


Figure 1b. d-MPH plasma profiles for CTx-1301 tablets (Treatments B and C)

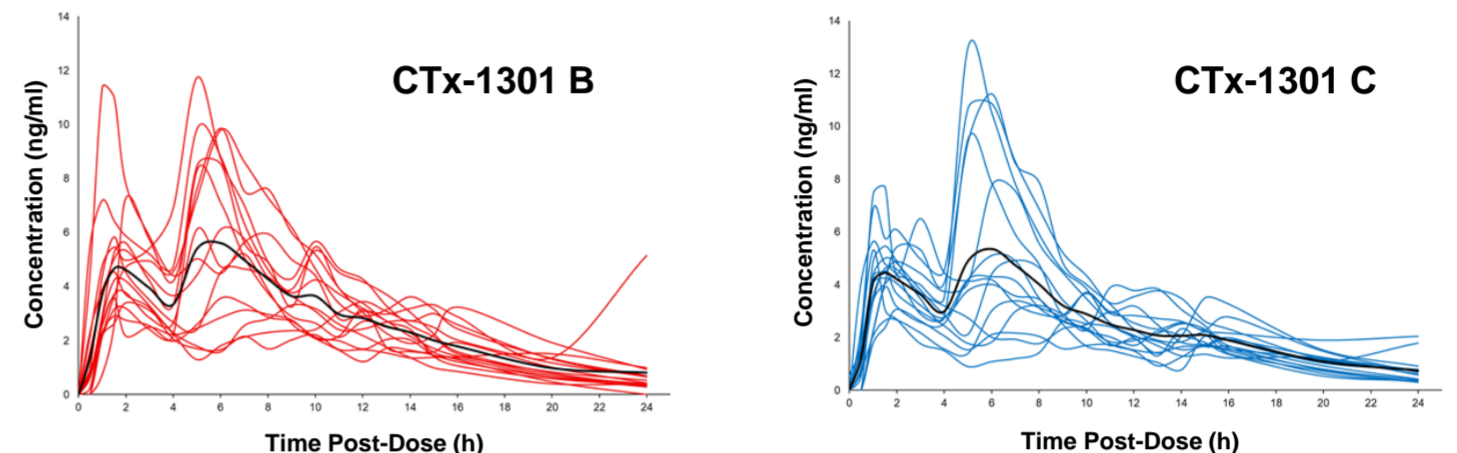


Figure 1c. d-MPH plasma profiles for Focalin[®] XR (Treatment A)

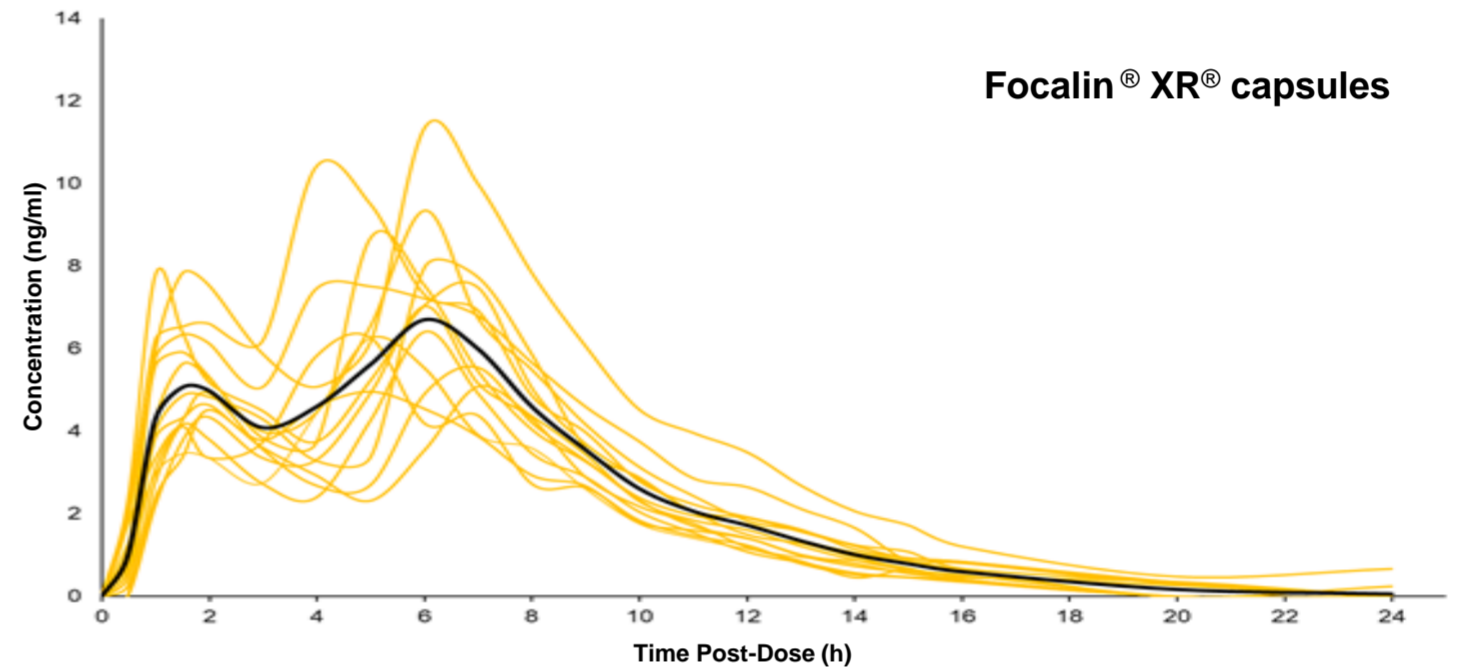


Table 1. Comparison of mean d-MPH Pharmacokinetic plasma profiles

| | 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 |
| C _{max(0-4h)} (ng/ml) | 4.9 (91%) | 5.2 (96%) | 5.4 |
| T _{max} (h) | 1.6 | 1.9 | 2.3 |
| Half life (h) | 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

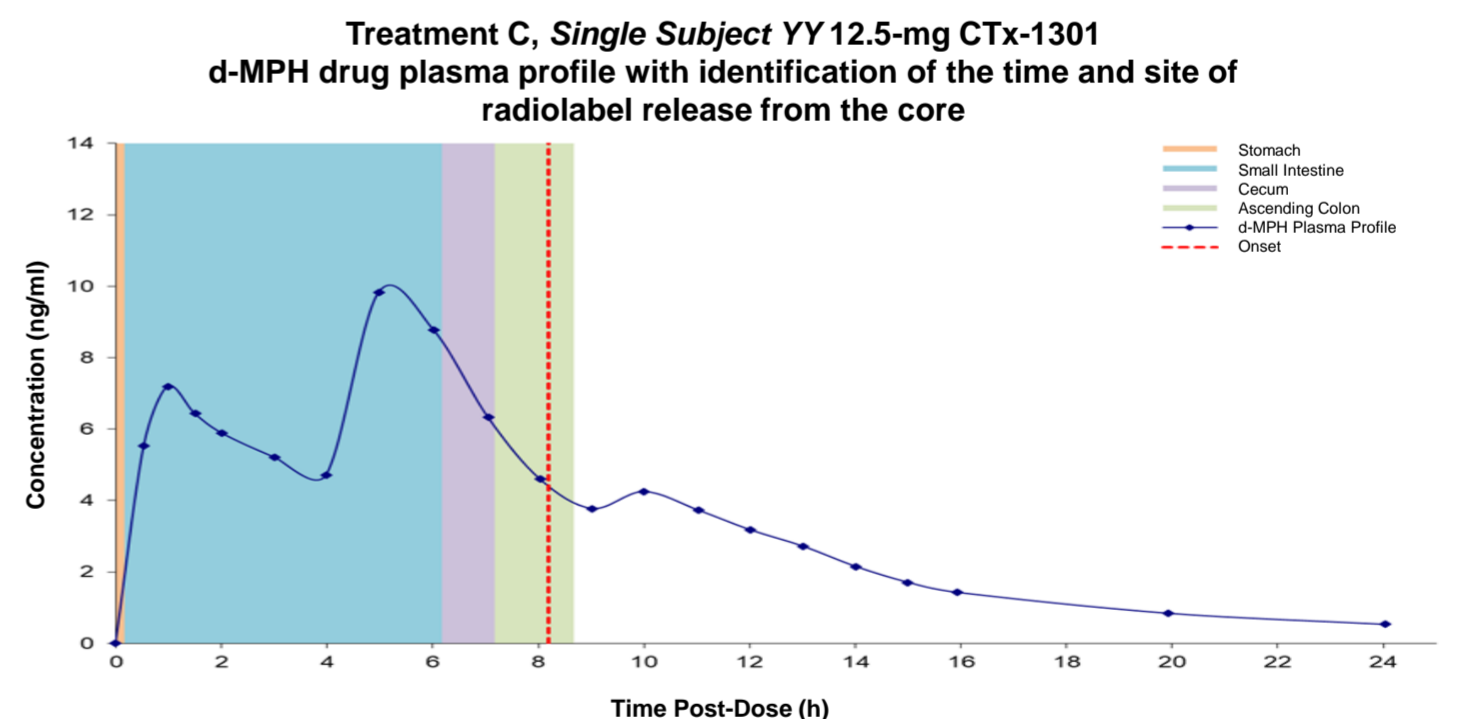
- Mean onset of radiolabel release of the third d-MPH release was at 10.3 ± 1.7 h; corresponds with the higher d-MPH plasma level AUC₍₈₋₂₄₎ hours
- Mean onset of radiolabel release for the second d-MPH release was at 4.7 ± 1.3 h; corresponds with T_{max(4-8)} (5.8 ± 1.2 h) for the second d-MPH plasma peak

Table 2. Final immediate release Core for individual patients

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

*values in () are the average

Figure 2. Example of Single Patient Composite profile with radiolabeled release from 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₍₈₋₂₄₎ 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

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

ACKNOWLEDGMENTS



Medical writing support was provided by MA3C GMBH (funded by Cingulate Therapeutics, LLC).

CONTACT INFORMATION:

Cingulate Therapeutics: 1901 W. 47th Place, Kansas City, KS 66205, +1 (913) 942-2300; info@ctxusa.com
 Bio-Images Drug Delivery, Glasgow Royal Infirmary, 84 Castle St., Glasgow G4 0SF, UK; +44 (0)141 552 8791; enquiries@bddpharma.com