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Development and *In Vivo* Pharmacoscintigraphic Evaluation of a Novel Triple-Release Dexmethylphenidate Hydrochloride Tablet for Improved Once Daily Dosing

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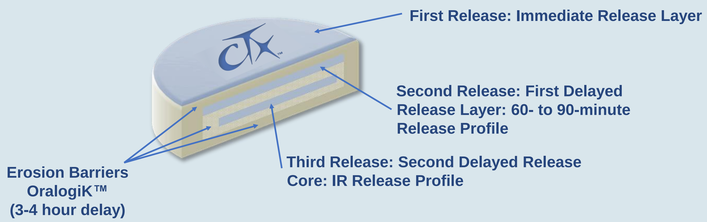
PURPOSE

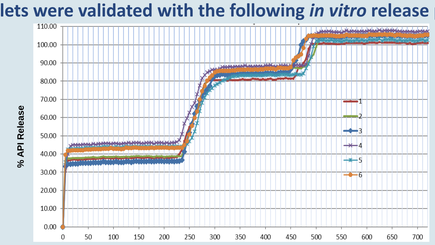
To design a novel triple-release dexmethylphenidate hydrochloride (d-MPH) tablet for once daily ADHD therapy with extended therapeutic plasma levels utilizing proprietary erosion barrier technology, assess in vivo performance using pharmacoscintigraphy, and compare pharmacokinetics with commercially available Focalin XR.



METHOD(S)

Study Design: A fasting, three-arm pharmacoscintigraphic study in healthy male volunteers compared the pharmacokinetics of the 12.5 mg CTx 1301 triple-release tablet and 10-mg Focalin XR capsules. Subjects received a single dose of the appropriate at approximately 9 AM on each treatment day.

CTx-1301 tablets were validated with the following *in vitro* release profile:



- **Treatment A: Commercially obtained 10-mg Focalin XR capsules (not radiolabelled)**
- **Treatments B & C: 12.5-mg CTx-1301 tablets radiolabelled (4 MBq technetium-99m) to visualise site and time of in vivo release (second or third release layers of the 12.5-mg CTx-1301 tablets)**
- **Subjects received one dose of each treatment under fasting conditions with dosing separated by a minimum of 7 days**
- **Sequential anterior and posterior abdominal images of 25 seconds duration were acquired using a Siemens eCam every 20 minutes until 14 hours post-dosing; pharmacokinetic blood sampling was carried out at defined intervals**
- **Plasma profiles were compared to time and site of radiolabel release for the 12.5-mg CTx-1301 tablets, and dose corrected pharmacokinetic parameters were compared across all formulations**

RESULT(S)

Radiolabelled 12.5-mg CTx-1301 tablets demonstrated:

- **Mean Onset of radiolabel release for the second d-MPH release was at 4.7 ± 1.3 hours; excellent correlation with $Tmax_{(4-8)}$ (5.8 ± 1.2 hr) for the second d-MPH plasma peak**
- **Mean onset of radiolabel release for the third d-MPH release was at 10.3 ± 1.7 hours; correlates with the higher d-MPH plasma level $AUC_{(8-24)}$ hours**

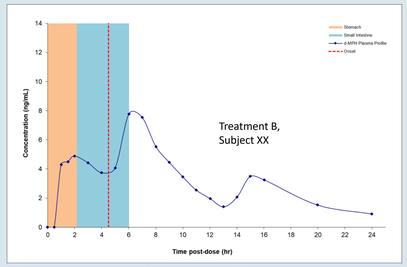


Figure 1. Composite of Treatment B, Subject XX 12.5-mg CTx-1301 d-MPH drug plasma profile with identification of the time/point of radiolabel release from the Second Release Layer

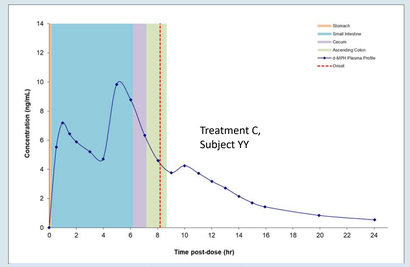


Figure 2. Composite of Treatment C, Subject YY 12.5-mg CTx-1301 d-MPH drug plasma profile with identification of the time/point of radiolabel release from the DR2

Table 1 Comparison of mean d-MPH Release PK parameters

Parameter	Focalin XR (Treatment A) Mean (Range)	CTx-1301 (Treatment B) Mean (Range)	CTx-1301 (Treatment C) Mean (Range)
d-MPH Release 1			
mean C_{max} (ng/mL)	5.4 (3.5 – 7.8)	4.9 (2.7 – 7.7)	5.2 (2.9 – 11.4)
mean $T_{max\ 0-4}$(hr)	1.6 (1.0 – 2.0)	1.6 (1.0 – 2.0)	1.7 (1.0 – 3.0)
Mean $AUC_{(0-4)}$	15.45 (10.4 – 23.8)	13.4 (7.7 – 20.5)	14.01 (8.4 – 26.9)
d-MPH Release 2			
mean C_{max} (ng/mL)	7.5 (5.0 – 11.4)	6.6 (2.2 – 13.0)	6.9 (2.2 – 11.7)
mean $T_{max\ 4-8}$(hr)	5.7 (4.0 – 7.0)	5.8 (4.0 – 8.0)	6.3 (5.0 – 8.0)
$AUC_{(4-8)}$	22.8 (14.6 – 33.9)	18.41 (4.6 – 35.9)	19.75 (7.4 – 33.0)
d-MPH Release 3[1] Mean AUC_{8-24} (ng-hr/mL)[2]	17.05	29.24	31.60
Mean AUC_{INF} (ng-hr/mL)[3]	71.25 (52.9 – 117.0)	63.86 (42.4 – 101.6)	67.74 (43.6 – 97.2)

[1] Focalin XR does not have a Third Release
[2] Determined by deducting $AUC_{(0-8)}$ from $AUC_{(0-last)}$
[3] 10-mg Focalin XR values normalized to 12.5 mg

- **C_{max} data from the IR release for all three Treatments of the study were comparable at 5.4, 4.9 and 5.2 ng/mL; confirming the initial 12.5-mg CTx-1301 IR layer released d-MPH in a similar manner to 10-mg Focalin XR**
- **The C_{max} for 12.5-mg CTx-1301 DR1 in Treatments B and C were approximately 10% lower at 6.6 and 6.9 ng/mL respectively when compared to the 10-mg Focalin XR C_{max} of 7.5 ng/mL, an expected result of the CTx-1301 sustained release profile**
- **The overall extent of absorption of the 12.5-mg CTx-1301 formulations were 89% and 95% (Treatments B&C) of 10-mg Focalin XR**
- **Mean exposure from 8 – 24 hours as determined by $AUC_{(8-24)}$ values for the 12.5-mg CTx-1301 tablets were significantly higher at 29.2 and 31.6 ng-hr/mL (1.7 – 1.85 greater) than the 10-mg Focalin XR (17.1 ng-hr/mL), confirming the 12.5-mg CTx-1301 tablet design produced higher drug levels for an extended period**

Figure 3 shows the d-MPH plasma profiles for Focalin XR (Treatment A), CTx-1301 tablets (Treatments B & C). Mean AUC values from 8-24 hours post-dose for the CTx-1301 tablets was significantly higher at 29.2 and 31.6 ng-hr/mL when compared to Focalin XR (17.1 ng-hr/mL), confirming the CTx-1301 tablet design produced the desired higher drug levels for a prolonged period.

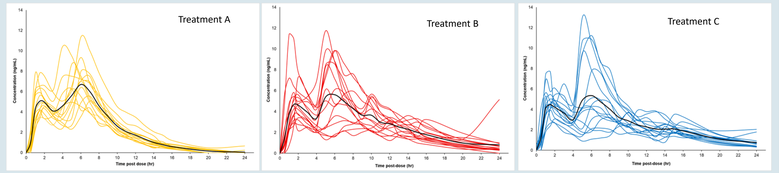


Figure 3: d-MPH plasma profiles for Focalin XR (Treatment A) and CTx-1301 tablets (Treatments B and C)

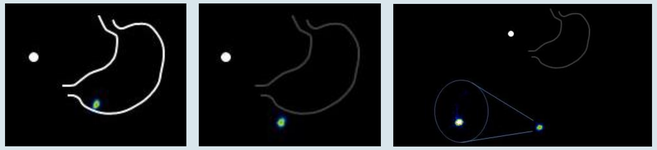


Figure 4: Example of scintigraphic data for 12.5-mg CTx-1301 2nd and 3rd release points (Treatments B and C)

CONCLUSION(S)

- ***The* d-MPH *in vitro* dissolution data correlated well with the *in vivo* release data of radiolabelled CTx-1301 tablets and with the pharmacokinetic profiles**
- **The overall extent of absorption of the 12.5-mg CTx-1301 formulations were 89% and 95% (Treatments B&C) of 10-mg Focalin XR**
- **The mean IR Layer Release Profile for the 12.5-mg CTx-1301 was similar to the IR Release Profile for the portion of the 10-mg Focalin XR**
- **The 2nd 12.5-mg CTx 1301 d-MPH release correlated with the CTx predicted delay time and was similar to the 2nd d-MPH 10-mg Focalin XR release**
- **The 3rd 12.5-mg CTx 1301 d-MPH release extended the plasma levels 4 – 6 hours when compared to 10-mg Focalin XR, confirming that the CTx-1301 tablet design strategy offers a potentially new treatment option for ADHD patients**

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