Abstract No

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In-vitro and In-vivo Assessment of a Novel Immediate Release Abuse Deterrent Dextroamphetamine Formulation

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PURPOSE

While effective in the treatment of ADHD, CNS stimulants have been shown in multiple studies to have a high risk for abuse. It has been reported that 40% or more of the people who misuse or abuse stimulants, particularly immediate-release (IR) stimulants, do so by snorting or injecting them[1].

Stimulants have significant adverse events. Rapid absorption and higher concentrations from intranasal (IN) and intravenous (IV) use are especially concerning. The addiction potential of controlled substances has been linked to their rate of brain penetration[2].

ADAIR is an oral, semisolid, liquid-filled, hard gelatin capsule formulation of dextroamphetamine sulfate. Using a liquid fill hard capsule allows the combination of highly viscous waxy materials with swelling/gelling polymers in high concentrations, to provide physical barriers for extraction/powdering etc. to deter abuse. This formulation type may have the potential to affect dissolution, and pharmacokinetics. However, through a careful selection of excipients which maximises the abuse deterrent properties without impacting on the pharmacokinetics, these risks are mitigated.

The abuse-deterrent properties of ADAIR have been previously reported[3], here we report the *in-vitro* and *in-vivo* performance of the ADAIR formulation.

METHOD(S)

Dissolution

In-vitro dissolution method development: dissolution assessment was based on USP dissolution method for dextroamphetamine sulfate tablet, using apparatus 1, basket speed of 100 rpm in 500 ml of 0.01M HCl at 37^{0}C. Samples were analysed using an Agilent HPLC system and XDB-C18 5um 250 mm x 4.6 mm at 210 nm. The mobile phase was sodium-1-hepatanesulfonate: dilute acetic acid: methanol (57.5:2.5:40 v/v/v).

Bioequivalence study

Phase I, single-dose, crossover bioequivalence study of 10 mg dextroamphetamine sulfate and 10 mg ADAIR in healthy subjects under fasting conditions was performed. A total of 24 subjects were enrolled in the study. Plasma was isolated and analysed for dextroamphetamine using a validated HPLC-MS/MS method.

Pharmacokinetics:

C_{max} (maximum plasma concentration)

AUC_{0-t} and $AUC_{0-\infty}$ (cumulative area under the concentration time curve)

Safety:

Adverse events (AE)
Clinical laboratory tests
Physical examination
Vital signs
Electrocardiograms (ECG)
Columbia Suicide Severity Rating Scale (C-SSRS)

RESULTS

Formulation Selection and In-vitro Dissolution

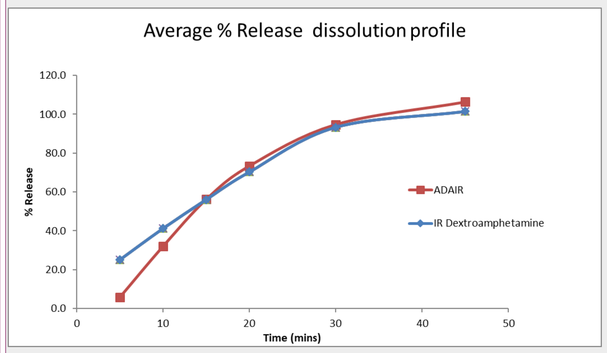
A range of Prototype formulations were designed, and screened for abuse deterrent properties. Those formulations that met the in-vitro abuse deterrence criteria were further evaluated for dissolution to identify the lead formulation (ADAIR, Table 1). Note, these were the early prototype formulations, the drug potency was somewhat higher for the tested batch. The full dissolution profile of the ADAIR formulation is compared with the Reference IR Dextroamphetamine (IR Dex) product (Figure 1).

Figure 1 shows a very close match of the dissolution profile of the ADAIR formulation vs IR Dex. The dissolution rate was a little slower for the ADAIR formulation relative to IR Dex at the 5min and 10min timepoints. This is likely attributable to a slight delay in the initial dissolution of the capsule shells. The release profile for ADAIR at 15min timepoint and beyond closely resembles that of IR Dextroamphetamine.

Table 1: Mean dissolution at 45 minutes

Formulations	% Release at 45min	
	Mean	%RSD
IR Dex	101.4%	1.6
ADAIR	106.3%	2.0
Prototype A	48.8%	9.9
Prototype B	14.0%	13.1
Prototype C	25.2%	14.4

Figure 1 Average ADAIR dissolution profile versus IR Dextroamphetamine product



Bioequivalence

Based on the in-vitro data, the final ADAIR formulation was defined and subjected to an in-vivo PK study.

Of the 24 subjects enrolled in the study, all 24 were included in the PK analysis, 22 met protocol specified criteria for inclusion in the statistical analysis population.

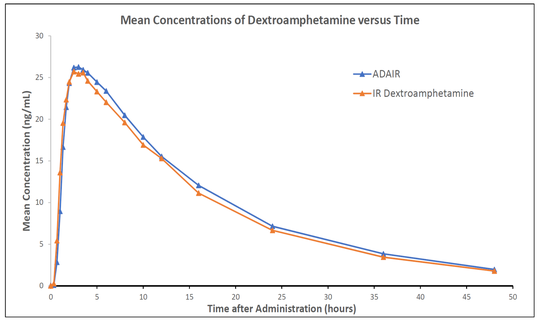
The statistical results indicate that the Test (ADAIR) to Reference (IR Dex) ratios of the geometric LS means of Cmax, (99.57%) AUC_{0-t} (103.82%) and $AUC_{0-\infty}$ (104.02%) were all near unity, with 90% confidence intervals for each parameter.

As the results were well within the 80-125% range, bioequivalence was demonstrated between ADAIR and IR dextroamphetamine sulfate under fasting conditions.

Table 2: Pharmacokinetic results

Parameter	Intra-subject C.V. %	Geometric LS means		Ratio (%)	90% Confidence Limit (%)	
		ADAIR	IR Dex		Lower	Upper
Cmax	5.0	27.145	27.262	99.57	96.98	102.23
AUC_{0-t}	8.2	467.437	450.241	103.82	99.47	108.38
$AUC_{0-\infty}$	8.9	503.698	484.347	104.00	99.28	108.94

Figure 2 Mean concentration of dextroamphetamine versus time



RESULTS

Safety Evaluation

- No serious adverse events (SAEs) were reported during this study.
- All treatment emergent adverse event (TEAEs) were mild in severity and resolved by close of study.
- No subjects discontinued due to an Adverse Event (AE).
- There were no clinically significant changes in ECGs, vital signs, C-SSRS or laboratory parameters observed.

The safety profile was consistent with known effects of stimulants with no evidence of any new safety signals.

CONCLUSIONS

Despite the challenges of formulating an abuse-deterrent product whilst maintaining the immediate release dissolution profiles, we have shown that this can be accomplished with a liquid fill capsule formulation of dextroamphetamine sulfate (ADAIR).

The ADAIR 10 mg capsule formulation has been shown to meet all of the bioequivalence criteria with the reference dextroamphetamine sulfate 10 mg IR tablet. In addition, the safety profile of the ADAIR formulation was consistent with the known effects of stimulants with no evidence of any new safety signals.

These results support further investigation of ADAIR as a potential, abuse-deterrent alternative to dextroamphetamine IR in the treatment of ADHD.

REFERENCES

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