Abuse-Deterrent Properties of a Novel Formulation of Immediate-Release Dextroamphetamine (ADAIR) Compared to Reference Dextroamphetamine IR

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BACKGROUND

CNS stimulants have been shown in multiple studies to have a high risk for abuse. Published studies report that 40% or more of people who misuse or abuse stimulants, particularly IR stimulants, do so by snorting (White 2006).

Rapid absorption and higher peak concentrations of stimulants from IN and IV use are especially concerning due to well-documented adverse event profiles and to addiction potential, which has been linked to rates of brain penetration (Samaha 2005).

ADAIR is a proprietary IR formulation of dextroamphetamine (dex) embedded in a thick gel inside a hard capsule and is designed to deter misuse and abuse by IN and IV routes of administration.

METHODS

VAL-103 was a phase 1, pilot, randomized, double-blind, active-controlled, 2-treatment crossover study. Objectives included assessing safety, PK, and PD of manipulated ADAIR 30 mg compared to crushed dex sulfate IR 30 mg (DEX) administered IN in non-dependent recreational stimulant users. The primary PD endpoint was mean maximum drug liking (Emax) on a bipolar 100mm VAS.

Sixteen qualified subjects demonstrated a confirmed positive response to stimulants and entered the treatment phase. Safety was assessed via AEs, vital signs, ECGs, safety labs and CSSR-S.

RESULTS

All 16 subjects completed the study and were included in the safety, PK and PD analyses.

SAFETY

The safety profile observed was consistent with the known profile of dex, with no new or unique safety concerns noted. No SAEs were reported.

PK

Manipulated IN ADAIR demonstrated an attenuated PK profile (i.e., lower Cmax, later tmax, and reduced AUC, especially in the early period post dose) compared to IN DEX.

PD

The primary PD endpoint (Drug Liking Emax) demonstrated manipulated IN ADAIR had significant reduction ($p<0.0001$) in drug liking compared with IN DEX.

Good drug effects were also significantly lower for manipulated IN ADAIR compared to IN DEX ($p=0.0016$)

Manipulated IN ADAIR demonstrated more negative effects particularly on the SRAII (e.g., nasal burning, discharge, and congestion) compared to IN DEX (all values $p<0.05$).

All other PD endpoints reflected abuse-deterrent properties for IN ADAIR relative to IN DEX (e.g., Take Drug Again Emax, High, Subjective Drug Value).

Subjects reported unwillingness to spend much time manipulating dex (IN DEX, mean = 11.4 min; IN ADAIR, mean = 9.3 min) This finding is consistent with reports for opioids, suggesting stimulant formulations requiring extensive manipulation may deter IN abuse (Sellers 2013).

DEMOGRAPHICS

	Statistic	Overall
Age (Years)		
	Number of Subjects	16
	Mean	41.7
	SD	7.43
	Median	42.5
	Min	26
	Max	50
Age Group		
	<18	0
	18-40	7 (43.8 %)
	41-64	9 (56.3 %)
	65-75	0
	>75	0

	Statistic	Overall
Gender		
	Female	3 (18.8 %)
	Male	13 (81.3 %)
Race		
	American Indian or Alaska Native	0
	Asian	0
	Black or African American	3 (18.8 %)
	Native Hawaiian or other Pacific Islander	0
	White	13 (81.3 %)
	Other	0

SAFETY

The side effect and safety profiles observed were consistent with the known profile of dextroamphetamine, with no new or unique safety concerns noted. No SAEs were reported. There were no clinically significant changes in labs, vital signs, ECGs or C-SSRS.

Treatment Emergent Adverse Events

System Organ Class MedDRA Preferred Term	DEX 30 mg IN (N=16) n (%)	ADAIR 30mg IN (N=16) n (%)	Total (N=16) n (%)
Number and percentage of subjects experienced at least one TEAE	13 (81.3%)	14 (87.5%)	16 (100%)
Gastrointestinal disorders	2 (12.5%)	1 (6.3%)	2 (12.5%)
Dry mouth	2 (12.5%)	1 (6.3%)	2 (12.5%)
General disorders and administration site conditions	1 (6.3%)	3 (18.8%)	3 (18.8%)
Discomfort	0	1 (6.3%)	1 (6.3%)
Energy increased	0	1 (6.3%)	1 (6.3%)
Facial pain	0	1 (6.3%)	1 (6.3%)
Fatigue	1 (6.3%)	0	1 (6.3%)
Feeling of relaxation	0	1 (6.3%)	1 (6.3%)
Injury, poisoning and procedural complications	1 (6.3%)	0	1 (6.3%)
Burns second degree	1 (6.3%)	0	1 (6.3%)

System Organ Class MedDRA Preferred Term	DEX 30 mg IN (N=16) n (%)	ADAIR 30mg IN (N=16) n (%)	Total (N=16) n (%)
Musculoskeletal and connective tissue disorders	0	1 (6.3%)	1 (6.3%)
Back pain	0	1 (6.3%)	1 (6.3%)
Nervous system disorders	2 (12.5%)	3 (18.8%)	4 (25.0%)
Headache	1 (6.3%)	3 (18.8%)	3 (18.8%)
Psychomotor hyperactivity	1 (6.3%)	0	1 (6.3%)
Psychiatric disorders	12 (75.0%)	9 (56.3%)	15 (93.8%)
Euphoric mood	11 (68.8%)	7 (43.8%)	13 (81.3%)
Hypervigilance	5 (31.3%)	4 (25.0%)	7 (43.8%)
Respiratory, thoracic and mediastinal disorders	3 (18.8%)	6 (37.5%)	9 (56.3%)
Nasal congestion	0	3 (18.8%)	3 (18.8%)
Nasal discomfort	0	2 (12.5%)	2 (12.5%)
Oropharyngeal discomfort	1 (6.3%)	0	1 (6.3%)
Rhinorrhoea	1 (6.3%)	4 (25.0%)	5 (31.3%)
Throat irritation	1 (6.3%)	0	1 (6.3%)
Vascular disorders	1 (6.3%)	0	1 (6.3%)
Hypotension	1 (6.3%)	0	1 (6.3%)

PHARMACOKINETICS

Manipulated IN ADAIR demonstrated an attenuated PK profile (lower Cmax, later tmax, reduced AUC especially in the early period post-dose) compared to crushed IN DEX.

Pharmacokinetics of Dextroamphetamine after Insufflation of Manipulated ADAIR versus Reference Dextroamphetamine IR

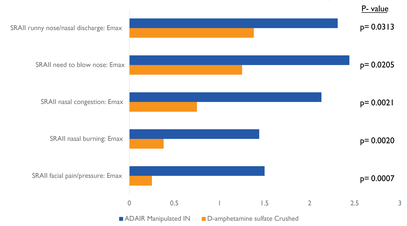
Parameter	Arithmetic Mean (%CV)		Geowmetric Least-Square Mean Ratio	90% Confidence Interval
	ADAIR	Dextroamphetamine IR		
C_{max} (ng/mL)	53.61 (24.5%)	63.44 (24.0%)	84.06	74.96 – 94.28
t_{max} (h)*	3.5 (1.25 - 6.0)	2.5 (1.5 - 5.0)	NA**	NA
AUC_{0-1h} (ng·h/mL)	13.53 (35.3%)	19.89 (31.1%	67.06	60.18 - 74.73
AUC_{0-2h} (ng·h/mL)	48.83 (33.9%)	66.59 (28.0%)	71.95	64.87 – 79.81
$AUC_{0-\infty}$ (ng·h/mL)	1038.6 (27.1%)	1203.6 (20.6%	84.68	76.38 – 94.28

*Median (range); **NA = not applicable

PHARMACODYNAMIC ASSESSMENTS - Subjected Rated Assessment of Intranasal Irritation (SRAII)

Subjects reported significantly more bad drug effects, including burning sensations, runny nose/nasal discharge, increased facial pain/pressure, and increased nasal congestion, after IN administration of ADAIR compared to DEX.

Subject - Rated Assessment of Intranasal Irritation (SRAII)

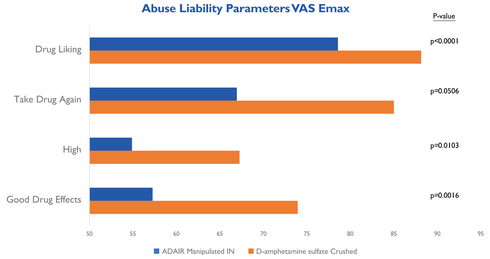


ABUSE LIABILITY PARAMETERS

The primary Abuse Liability endpoint (Drug Liking Emax) demonstrated that manipulated IN ADAIR had highly statistically significant ($p<0.0001$) reduction in drug liking compared with crushed IN DEX.

Reductions were also demonstrated for overall drug liking and for desire to take drug again for IN ADAIR compared to IN DEX. Other Abuse Liability endpoints demonstrated diminished positive drug effects including reduced "high", and fewer good drug effects of ADAIR vs DEX.

Abuse Liability Parameters VAS Emax



WLLINGNESS TO MANIPULATE

When subjects were asked how much time they were willing to spend to manipulate the two formulations to achieve the desired effect, they reported a mean of 11.2 mins for DEX and 9.3 mins for ADAIR. This finding is consistent with reports for opioids, suggesting that stimulant formulations requiring extensive manipulation may deter IN abuse (Sellers 2013).

CONCLUSIONS

- ADAIR was generally well tolerated, with no new or unique safety signals identified.
- ADAIR demonstrated an attenuated PK profile (lower Cmax, later tmax, reduced early AUC) compared to IN DEX.
- Drug Liking Emax demonstrated that recreational stimulant users liked manipulated IN ADAIR significantly less than crushed IN DEX.
- Additional Abuse Liability endpoints demonstrated less liking and good effects and significantly more bad effects of manipulated IN ADAIR vs crushed IN DEX.
- Recreational drug users were not willing to spend much time to manipulate IR stimulants for snorting, whereas the time required for manipulation of ADAIR to a substance that can be insufflated is substantial.
- These results support further investigation of ADAIR as a potential, abuse-deterrent alternative to other IR amphetamines (Adderall, Dexedrine) in the treatment of ADHD.

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