Inhaled Alprazolam, a Potential Rescue Medication, Works Rapidly in Patients with Photosensitive Epilepsy

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ALEXZA PHARMACEUTICALS

ABSTRACT

Objective
Evaluate ability of inhaled alprazolam to rapidly suppress photosensitivity in a double blind placebo-controlled crossover proof of concept study.
Background
Alprazolam formulated as an inhaled preparation (Staccato Alprazolam) could represent a rapidly effective rescue medication for epilepsy patients. Time to effect can be assessed in patients with photosensitive epilepsy, in whom epileptiform activity can be elicited at will.
Design/Methods
Patients ≥ 18 y.o. with photosensitive epilepsy at 3 sites were tested on a baseline day, and then received in randomized order either inhaled placebo (on 2 days) or 0.5, 1 or 2 mg inhaled alprazolam delivered using a hand-held Staccato device. Study days were separated by at least 1 week. Presence (and degree) of photosensitivity was measured predose, then at 2 min, 10 min, 30 min, 1, 2, 4 and 6 hours post-dose. Plasma concentration of study drug was measured at each time point. Sedation was assessed at each time point using the 100-mm linear visual analogue scale (VAS).
Results
Five patients were enrolled and completed all treatment arms. All doses decreased the mean standardized photosensitivity range (SPR), with maximal or near-maximal effect occurring by 2 minutes post dose. Higher doses produced effects on SPR out to 4 hours. Sedation was dose related, but separated from SPR effects at later 6 time points. Treatment was well tolerated with no serious adverse events.
Conclusions
Results from this study suggest that inhaled alprazolam strongly suppresses epileptiform activity within 2 minutes. Duration of effect was dose related, as was sedation. This data supports the possibility that inhaled alprazolam might have utility in stopping a seizure within 2 minutes of use.

INTRODUCTION

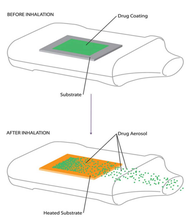
Alprazolam formulated as an inhaled preparation (Staccato Alprazolam) could represent a rapidly effective rescue medication for epilepsy patients

A phase 2 proof-of-concept trial with Staccato Alprazolam was conducted in epilepsy patients using Intermittent Photic Stimulation Model

Model used to assess effects of potential AEDs in a controlled laboratory setting, by way of measuring epileptiform changes on electroencephalogram (EEG)

STACCATO DRUG DELIVERY TECHNOLOGY

The Staccato System delivers drug quickly and reliably via oral inhalation; designed for systemic drug delivery



Single, normal breath delivers the drug
- Easy to use, hand-held device
- No coordination required

Aerosol is thermally generated
- Excipient-free drug is transformed into aerosol that is appropriately-sized for deep lung delivery
- Aerosol generation/ delivery in <0.5 seconds
- Systemic absorption via deep lung

Delivers IV pharmacokinetics
- Rapid absorption into bloodstream
- High bioavailability of emitted dose (>90%)

Staccato technology is approved in US and EU (ADASUVE®)

Three previously completed clinical trials demonstrated safety and tolerability of inhaled alprazolam <N>100)

STUDY OBJECTIVES

- To assess the effects of inhaled alprazolam on the IPS-induced photoparoxysmal EEG response in patients with epilepsy
- To correlate plasma concentrations of inhaled alprazolam with pharmacodynamic effects on IPS and sedation (PK/PD correlation)
- To assess the sedative properties of these doses in order to select maximally-effective dose with the least sedation for further clinical studies
- To assess the safety of a single dose of inhaled alprazolam in patients with photosensitive epilepsy

STUDY DESIGN/ METHODS

Randomized, multicenter, placebo-controlled, double-blind, 5-way crossover study

Evaluated patients with epilepsy using Intermittent Photic Stimulation (IPS) model

5 Patients Screened In-clinic

Each subject received three active doses and two placebo doses in a randomized order and administered during each of the five visits.

Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5

21 days | 7 to 28 days between each dose

Primary Endpoint
Change in Standardized Photosensitivity Range (SPR) in subjects receiving each dose of Staccato Alprazolam

Secondary Study Endpoints
- Assessment of sedation and somnolence using 2 visual analogue scales
- Correlation of plasma concentrations of *Staccato* Alprazolam with PD effects on the SPR range
- Correlation of plasma concentrations of *Staccato* Alprazolam with PD effects on sedation
- Assessment of adverse events and changes in the neurological examination

Description of Photosensitivity Model

Flash freq in Hz	2	5	8	10	13	15	18	20	23	25	30	40	50	60
	-	-	-	+	+	+	+	+	+	+	-	-	-	

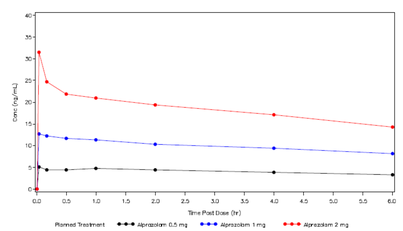
Patient is exposed to intermittent photic stimulation (14 frequencies, from 2 to 60 Hz)
- Start with lowest frequency and increase frequency stepwise until photosensitivity response elicited
- Repeat with highest frequency and decrease frequency

Quantitative measure is Standardized photosensitive range (SPR)
- Maximum SPR is 14
- In the example shown, SPR is 8

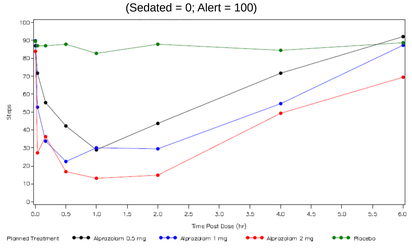
Primary endpoint is reduction in mean SPR – indication of antiseizure activity
Goal is enroll patients that have a relatively stable SPR – allows for small sample size

RESULTS: PK AND SEDATION

Pharmacokinetic Data Demonstrated Dose Proportionality

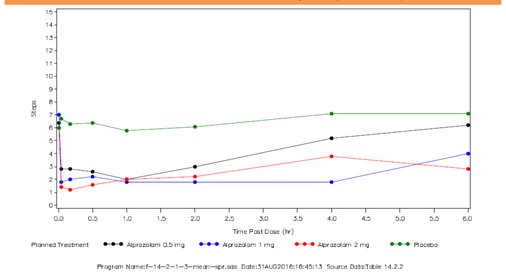


Dose Related Sedation and Duration of Sedation
(Sedated = 0; Alert = 100)

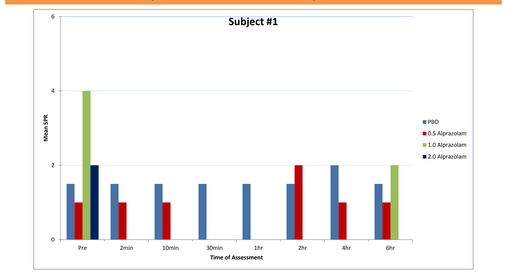


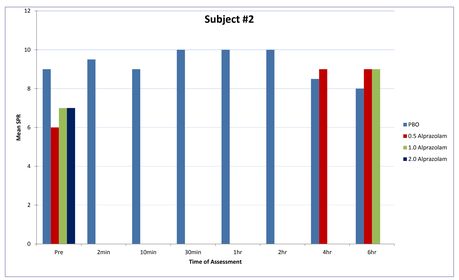
RESULTS: STANDARDIZED PHOTOSENSITIVITY RANGE (SPR)

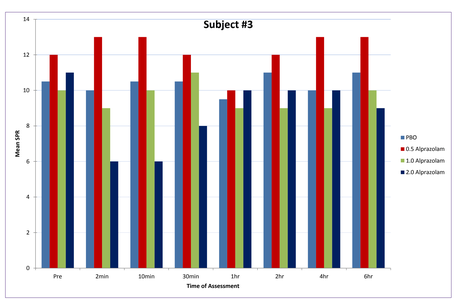
All 3 inhaled alprazolam doses produced a maximal or near-maximal decrease in mean SPR within the 1st time point (2 minutes)

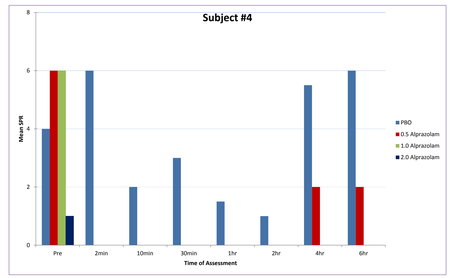


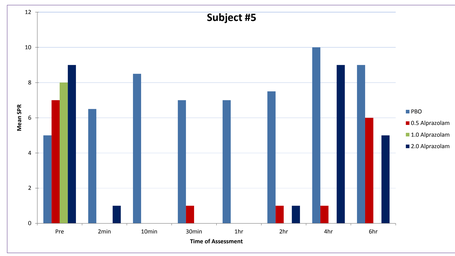
Complete abolishment of photosensitivity with all 3 active doses of inhaled alprazolam was seen in 4/5 patients.











ADVERSE EVENTS

- Treatment was well-tolerated
- Expected CNS adverse events (primarily sedation and somnolence

System Order Class	Placebo	0.5 mg	1 mg	2 mg	Overall
Eye	0	1	1	1	1
Gastrointestinal	1	2	2	2	2
Respiratory	0	2	1	2	2
Nervous system	1	2	3	4	4
• Amnesia	0	0	0	1	1
• Dizziness	0	1	0	0	1
• Headache	1	1	0	0	2
• Sedation	0	0	1	2	2
• Somnolence	1	1	2	2	2

SUMMARY AND CONCLUSIONS

All 3 inhaled alprazolam doses produced a decrease in mean SPR (primary endpoint)
- For all doses, maximal or near-maximal effect occurred by 2 minutes
- Magnitude and duration of effect was comparable for 1 mg and 2 mg

Dose related changes observed in the visual-analogue scale (VAS) for sedation and sleepiness
- Important marker for potential adverse events associated with dosing

PK analysis showed dose proportionality with plasma concentrations

Treatment was well-tolerated
- Expected CNS adverse events (primarily sedation and somnolence)

Effect on SPR suggests potential for rapid anti-seizure effect (within 2 minutes) and therefore the possibility that inhaled alprazolam might have utility in rapidly stopping a seizure event