Inhalation as an Efficient Delivery Route of Alprazolam for the Treatment of Acute Seizures: Randomized Study of Staccato® Alprazolam Relative to Oral Alprazolam

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Background

- Alprazolam is a benzodiazepine derivative indicated for the management of anxiety and panic disorders. Oral alprazolam was initially approved in the United States in 1981.[1]
- Staccato® alprazolam is a hand-held device that can provide rapid systemic delivery of alprazolam via inhalation, with the potential to provide rapid and early seizure termination.[2-4]

Objective

- To compare the plasma concentration of alprazolam following administration via inhalation with the Staccato® device relative to oral alprazolam administration using data from a Phase I clinical trial.

Methods

TRIAL DESIGN

- UP0104 (NCT05626439) was a Phase I, single-center, open-label, randomized, single-dose, 2-way crossover trial evaluating the bioavailability of alprazolam following Staccato® alprazolam 2 mg relative to oral alprazolam 2 mg in healthy adult participants (aged 18-55 years).
- The trial comprised a screening period, two 5-day treatment periods in which the study drug was administered as a single dose on day 1, and a safety follow-up visit within 7 (±2) days after the second administration of study drug.
- On day 1 of the first treatment period, participants were randomized 1:1 to treatment sequence AB or BA (A: Staccato® alprazolam 2 mg; B: oral alprazolam 2 mg).
- Blood samples for determining plasma concentration of alprazolam and its metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam) were collected pre-dose (within 30 minutes before dosing), at 2, 5, 10, 20, 30, and 45 minutes post-dose, and 1, 1.5, 2, 4, 6, 12, 24, 36, 48, 60, and 72 hours post-dose.
- Urine samples for determination of alprazolam levels were collected pre-dose (within 1 hour before dosing), and within the time intervals 0 to ≤12, 12 to ≤24, 24 to ≤36, 36 to ≤48, and 48 to ≤72 hours post-dose.

ANALYSES

- The pharmacokinetic (PK) parameters assessed in this analysis included: plasma concentrations of alprazolam and its metabolites; maximum plasma concentration (C_{max}); area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf}); apparent volume of distribution (V_z/F); apparent total body clearance (CL/F); fraction of the dose excreted unchanged in the urine (F_e); and renal clearance (CL_R).
  - Metabolite analyses also included the metabolite-to-parent ratio (MR) for AUC_{inf} and C_{max}.
- Statistical analyses between treatment groups in PK parameters were conducted using analysis of variance (ANOVA).
  - Point estimates for the ratio (Staccato® alprazolam/oral alprazolam) of geometric means (GeoMean) between the two treatments and the respective 2-sided 95% confidence intervals were calculated.

Results

PARTICIPANT DISPOSITION AND BASELINE DEMOGRAPHICS

- Overall, 53 participants were screened; 31 did not meet the eligibility criteria and 1 withdrew.
  - 21 participants were randomized to treatment (11 in sequence AB and 10 in sequence BA).
  - Most participants (20/21; 95.2%) completed the study; 1 (4.8%) participant discontinued from treatment sequence AB (after treatment period 1) due to an adverse event (hypotension) and was replaced.

Baseline demographics (ASPS)

	TREATMENT SEQUENCE		ALL PARTICIPANTS (N=21)
	AB (n=11)	BA (n=10)	
Age, mean (SD), years	40.3 (9.2)	37.4 (10.7)	38.9 (9.8)
Male, n (%)	6 (54.5)	5 (50.0)	11 (52.4)
Weight, mean (SD), kg	75.32 (11.50)	78.48 (13.73)	76.82 (12.39)
Height, mean (SD), cm	170.64 (7.41)	170.20 (9.64)	170.43 (8.32)
BMI, mean (SD), kg/m²	25.98 (4.53)	27.09 (4.19)	26.51 (4.30)
Racial group, n (%)			
Black	8 (72.7)	7 (70.0)	15 (71.4)
White	3 (27.3)	3 (30.0)	6 (28.6)

Treatment sequence AB was is assigned to participants randomized to receive Staccato® alprazolam 2 mg followed by oral alprazolam 2 mg. Treatment sequence BA was assigned to participants randomized to receive oral alprazolam 2 mg followed by Staccato® alprazolam 2 mg. ASPS, all study participants set; BMI, body mass index.

Overview

QUESTION

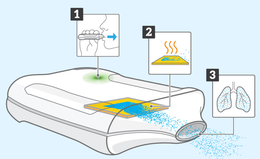
How does the plasma concentration of alprazolam compare following administration with the Staccato® device relative to oral administration?

INVESTIGATION

UP0104 (NCT05626439) was a Phase I, single-center, open-label, randomized, single-dose, 2-way crossover trial evaluating the bioavailability of alprazolam following Staccato® alprazolam 2 mg relative to oral alprazolam 2 mg in healthy adult participants (aged 18-55 years). Blood and urine samples were collected pre- and post-dose. Pharmacokinetic (PK) parameters of alprazolam and its metabolites were assessed.

The Staccato® alprazolam device

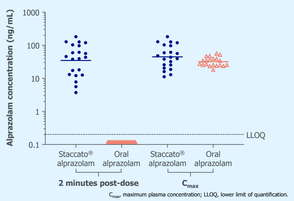
A single normal breath by the patient (**1**) will actuate the device and trigger instantaneous heating of the heat package (**2**) to form an aerosol of pure alprazolam that will directly reach the deep lung for fast systemic absorption (**3**).



RESULTS

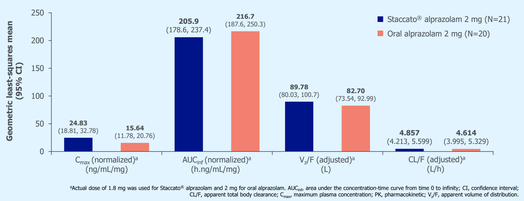
Following administration of **Staccato® alprazolam 2 mg**, the **plasma levels of alprazolam** at **2 minutes post-dose** were considered to be **clinically relevant** as they were usually similar or higher than those observed for C_{max} with oral alprazolam 2 mg.

Participant plasma alprazolam concentration



C_{max}, maximum plasma concentration; LLOQ, lower limit of quantification.

Plasma PK parameters of alprazolam



[a]Actual dose of 1.8 mg was used for Staccato® alprazolam and 2 mg for oral alprazolam. AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; V_z/F, apparent volume of distribution.

CONCLUSIONS

The distribution and elimination of alprazolam following administration by inhalation were comparable to those observed after oral administration. Absorption following inhalation with the Staccato® device was very fast and showed that plasma alprazolam concentrations achieved within 2 minutes post-dose were considered to be clinically relevant as they were usually similar or higher than those observed for C_{max} with oral alprazolam 2 mg. Thus, alprazolam administration via the Staccato® device is an efficient delivery route as treatment for rapid and early seizure termination.

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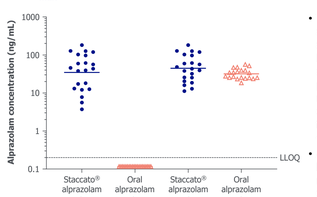
PLASMA PK PARAMETERS OF ALPRAZOLAM

Participant plasma alprazolam concentrations at 2 minutes post-dose and C_{max} for Staccato® alprazolam 2 mg and oral alprazolam 2 mg (PKS)



Lines represent geometric mean. LLOQ for alprazolam is 0.200 ng/mL. Alprazolam concentrations for oral alprazolam 2 mg were all below LLOQ at 2 minutes post-dose and were replaced by a value of LLOQ/2 in this graph. C_{max}, maximum plasma concentration; LLOQ, lower limit of quantification; PKS, pharmacokinetic set.

- The Staccato® device enables a rapid systemic delivery of alprazolam as demonstrated by plasma concentrations achieved at 2 minutes post-dose (median time to maximum plasma concentration of 2 minutes for Staccato® alprazolam vs 45 minutes for oral alprazolam).
- At this timepoint, alprazolam levels were in a clinically relevant range relative to C_{max} reached with oral alprazolam 2 mg.

- The GeoMean C_{max} of Staccato® alprazolam 2 mg was higher than oral alprazolam 2 mg (44.57 vs 31.78 ng/mL, respectively).
- The GeoMean AUC_{inf} of Staccato® alprazolam 2 mg was lower than oral alprazolam 2 mg (370.1 vs 433.9 h.ng/mL, respectively).
- The Staccato® device delivers 90% of the loaded dose.
  - Accounting for the actual dose delivered by the Staccato® device, the dose-normalized C_{max} and AUC_{inf} geometric least-squares mean Staccato® alprazolam/oral alprazolam ratios were 1.5876 and 0.9500, respectively.
- V_z/F and CL/F corrected for the adjusted dose of Staccato® alprazolam were similar between both treatments. V_z/F for Staccato® alprazolam 2 mg and oral alprazolam 2 mg was 89.78 L and 82.70 L, respectively. CL/F for Staccato® alprazolam 2 mg and oral alprazolam 2 mg was 4.857 L/h and 4.614 L/h, respectively.

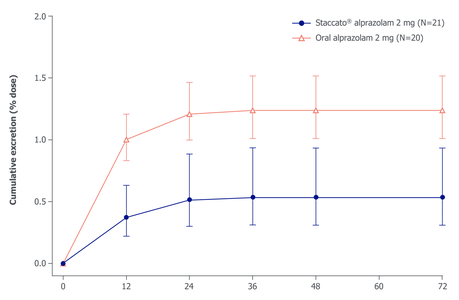
Plasma PK parameters of alprazolam with associated ANOVA (PKS)

	STACCATO® ALPRAZOLAM 2 mg (N=21)	ORAL ALPRAZOLAM 2 mg (N=20)
Based on nominal dose[a], GeoMean (GeoCV %)		
C_{max}, ng/mL	44.57 (97.4)	31.78 (31.7)
t_{max}, minutes	2.0 (2, 120)[b]	45.0 (20, 358)[b]
AUC_{inf}, h.ng/mL	370.1 (33.0)	433.9 (32.5)
V_z/F, L	99.99 (32.5)	82.73 (19.1)
CL/F, L/h	5.403 (33.0)	4.609 (32.5)
Based on normalized dose[c]		
$C_{max,\ norm}$, GeoLSM (95% CI), ng/mL/mg	24.83 (18.81, 32.78)	15.64 (11.78, 20.76)
GeoLSM ratio (95% CI)[d]	1.5876 (1.1658, 2.1619)	
Intraparticipant CV, %	49.4	
$AUC_{inf,\ norm}$, GeoLSM (95% CI), h.ng/mL/mg	205.9 (178.6, 237.4)	216.7 (187.6, 250.3)
GeoLSM ratio (95% CI)[d]	0.9500 (0.8391, 1.0757)	
Intraparticipant CV, %	19.0	
Based on adjusted dose[c]		
V_z/F, GeoLSM (95% CI), L	89.78 (80.03, 100.7)	82.70 (73.54, 92.99)
GeoLSM ratio (95% CI)[d]	1.0856 (0.9537, 1.2358)	
Intraparticipant CV, %	19.9	
CL/F, GeoLSM (95% CI), L/h	4.857 (4.213, 5.599)	4.614 (3.995, 5.329)
GeoLSM ratio (95% CI)[d]	1.0526 (0.9297, 1.1918)	
Intraparticipant CV, %	19.0	

[a]2 mg for both Staccato® and oral alprazolam; [b]Data are median (minimum, maximum); [c]Actual dose of 1.8 mg was used for Staccato® alprazolam and 2 mg for oral alprazolam; [d]Ratio is Staccato® alprazolam/oral alprazolam. ANOVA, analysis of variance; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; GeoCV, geometric coefficient of variation; GeoLSM, geometric least-squares mean; GeoMean, geometric mean; norm, normalized; PK, pharmacokinetic; PKS, pharmacokinetic set; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

URINE PK PARAMETERS OF ALPRAZOLAM

Cumulative fraction of urinary excretion of alprazolam (PKS)[a]



Geometric means are presented with 95% confidence intervals of the geometric mean. [a]Based on adjusted dose (actual dose of 1.8 mg was used for Staccato® alprazolam and 2 mg for oral alprazolam). PKS, pharmacokinetic set.

- F_e was very low and accounted for 0.5362% (dose-adjusted) and 1.238% of the dose for Staccato® alprazolam 2 mg and oral alprazolam 2 mg, respectively.
  - In both treatments, more than half of the total cumulative amount of alprazolam was excreted in the urine during the first 12 hours post-dose, and urinary excretion was completed 24-36 hours post-dose.
- The GeoMean CL_R was lower with Staccato® alprazolam 2 mg (0.02607 L/h) relative to oral alprazolam 2 mg (0.05706 L/h) but was more variable (geometric coefficient of variation of 186.7% and 67.1%, respectively).

PLASMA PK PARAMETERS OF METABOLITES

Metabolite-to-parent ratios of alprazolam metabolites with associated ANOVA (PKS)

	STACCATO® ALPRAZOLAM 2 mg (N=21)	ORAL ALPRAZOLAM 2 mg (N=20)
4-hydroxyalprazolam		
MR-AUC_{inf}, GeoLSM (95% CI)	0.09890 (0.08321, 0.1176)[a]	0.1120 (0.09411, 0.1332)[b]
GeoLSM ratio (95% CI)[c]	0.8833 (0.8413, 0.9275)	
Intraparticipant CV, %	6.2	
MR-C_{max}, GeoLSM (95% CI)	0.02595 (0.02024, 0.03328)	0.06282 (0.04875, 0.08096)
GeoLSM ratio (95% CI)[c]	0.4131 (0.3155, 0.5407)	
Intraparticipant CV, %	42.6	
α-hydroxyalprazolam		
MR-AUC_{inf}, GeoLSM (95% CI)	0.02554 (0.02148, 0.03036)[a]	0.02839 (0.02392, 0.03371)[d]
GeoLSM ratio (95% CI)[c]	0.8994 (0.8316, 0.9728)	
Intraparticipant CV, %	9.1	
MR-C_{max}, GeoLSM (95% CI)	0.007290 (0.005794, 0.009172)	0.02278 (0.01801, 0.02881)
GeoLSM ratio (95% CI)[c]	0.3200 (0.2424, 0.4224)	
Intraparticipant CV, %	43.7	

[a]n=20; [b]n=16; [c]Ratio is Staccato® alprazolam/oral alprazolam; [d]n=18. ANOVA, analysis of variance; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GeoLSM, geometric least-squares mean; MR, metabolite-to-parent ratio; PKS, pharmacokinetic set.

- For both 4-hydroxyalprazolam and α-hydroxyalprazolam, the metabolite-to-parent ratios based on C_{max} were lower for Staccato® alprazolam 2 mg than oral alprazolam 2 mg.
- For 4-hydroxyalprazolam, the metabolite-to-parent ratio based on AUC_{inf} was lower for Staccato® alprazolam 2 mg than oral alprazolam 2 mg.
  - No notable difference between the two treatments in the metabolite-to-parent ratio based on AUC_{inf} was observed for α-hydroxyalprazolam.

SAFETY AND TOLERABILITY (SS)

- Overall, 7 (33.3%) participants reported a total of 12 treatment-emergent adverse events (TEAEs) and 5 (23.8%) participants reported drug-related TEAEs (all with Staccato® alprazolam 2 mg). No severe TEAEs, serious TEAEs, or deaths were reported.
- The most common TEAEs were decreased oxygen saturation and lethargy reported in 4 (19.0%) and 3 (14.3%) participants, respectively.
- TEAEs of decreased oxygen saturation generally occurred with lethargy (3 participants) or somnolence (1 participant) as the participants were falling asleep, leading to shallow breathing.
- One participant (4.8%) discontinued due to a TEAE of hypotension, which was considered non-serious, moderate in intensity, related to Staccato® alprazolam 2 mg, and was resolved after receiving a saline infusion.

Conclusions

- The distribution and elimination of alprazolam following administration by inhalation were comparable with those observed after oral administration.
- Absorption following inhalation with the Staccato® device was very fast and showed that plasma alprazolam concentrations achieved within 2 minutes post-dose were considered to be clinically relevant as they were usually similar or higher than those observed for C_{max} with oral alprazolam 2 mg.
- Thus, alprazolam administration via the Staccato® device is an efficient delivery route as treatment for rapid and early seizure termination.[2-4]

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