Poster P336

Pulmonary safety of Staccato® alprazolam in healthy participants and participants with mild asthma: phase 1, randomised, double-blind, placebo-controlled trial

S David Miller[1]
Craig F LaForce[2]
Laura Barlow[3]
Aliceson King[4]
Maria Burian[5]
Hugues Chanteux[5]

1. Northeast Medical Research Associates, North Dartmouth, MA, USA
2. North Carolina Clinical Research, Raleigh, NC, USA
3. Veramed, Twickenham, UK
4. UCB Pharma, Smyrna, GA, USA
5. UCB Pharma, Braine l'Alleud, Belgium

Overview

QUESTION

What is the pulmonary safety of repeat dosing of Staccato® alprazolam in healthy participants and those with mild asthma?

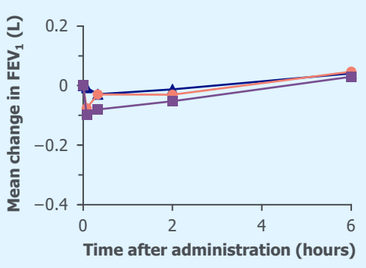
INVESTIGATION

Phase I, randomised, double-blind, placebo-controlled trial (UP0099; NCT04802746) evaluating 2 consecutive doses of Staccato® alprazolam administered 72 hours apart (day 1 and day 4) in adults. Part A: Staccato® alprazolam 1 mg and 2 mg vs placebo in healthy participants. Part B: Staccato® alprazolam 2 mg vs placebo in participants with mild asthma.

RESULTS

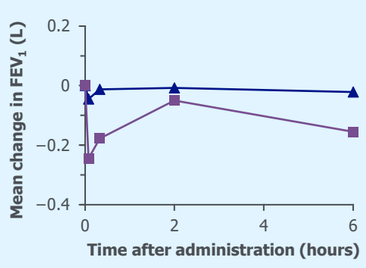
Spirometry

Part A: Healthy participants (day 1)



- **FEV_1** values showed greater decrease vs placebo for Staccato® alprazolam 1 mg and 2 mg at 5 minutes post-dose, and for Staccato® alprazolam 2 mg at 20 minutes post-dose.
- **FVC** values decreased from baseline at 5 minutes post-dose with Staccato® alprazolam 1 mg, and up to 2 hours post-dose with Staccato® alprazolam 2 mg.
- For both **FEV_1** and **FVC**, observed differences vs placebo were statistically significant but not considered clinically relevant.
- No major changes in **FEV_1/FVC** ratios were observed after any study treatments, and no statistically significant differences were observed.

Part B: Participants with mild asthma (day 1)



- **FEV_1** values showed a greater decrease with Staccato® alprazolam 2 mg vs placebo at 5 and 20 minutes post-dose.
- **FVC** values decreased from baseline at all post-dose time points; these decreases were more pronounced with Staccato® alprazolam 2 mg than placebo at 5 and 20 minutes post-dose.
- For both **FEV_1** and **FVC**, observed differences vs placebo were statistically significant but not considered clinically relevant.
- No major changes in **FEV_1/FVC** were observed after any study treatment. A statistically significant negative difference vs placebo was observed at 5 minutes post-dose.

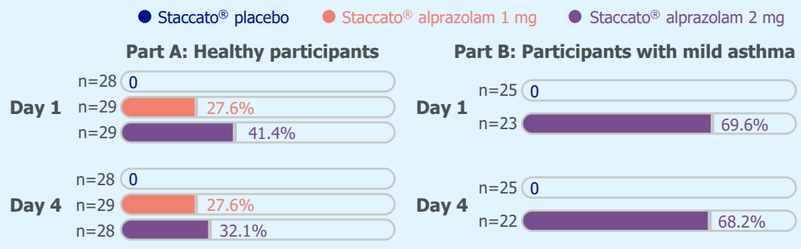
Staccato® placebo — Staccato® alprazolam 1 mg — Staccato® alprazolam 2 mg

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Tolerability

Incidence of respiratory TEAEs

Most of the respiratory TEAEs were cough



TEAE, treatment-emergent adverse event.

CONCLUSIONS

Two doses of Staccato® alprazolam (either 1 mg or 2 mg) administered 72 hours apart were well tolerated in healthy participants and those with mild asthma. Minor decreases in forced expiratory volume in 1 second (FEV_1) from baseline were observed with Staccato® alprazolam vs placebo at several time points; however, these were not considered clinically relevant and there was no further exacerbation (steeper FEV_1 decrease) following repeat dosing. There was no evidence of airway obstruction related to Staccato® alprazolam.

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Background

- Staccato® alprazolam is a hand-held device that can provide rapid systemic delivery of alprazolam via inhalation.
- A previous clinical trial has shown Staccato® alprazolam to be efficacious at achieving seizure activity cessation within 2 minutes of administration without recurrence of seizure activity within 2 hours.[1]
- It is important to assess the potential of Staccato® alprazolam for drug-induced bronchospasm.

Objective

- To evaluate the pulmonary safety of repeat dosing of Staccato® alprazolam in healthy participants and those with mild asthma.

Methods

TRIAL DESIGN

- UP0099 (NCT04802746) was a Phase I, randomised, double-blind, placebo-controlled safety trial evaluating 2 consecutive doses of Staccato® alprazolam administered 72 hours apart (day 1 and day 4) in adult participants aged 18-55 years.
- The trial was conducted in 2 parts at the same 2 sites in the United States:
  - Part A evaluated 2 dose levels (1 mg and 2 mg) of Staccato® alprazolam vs Staccato® placebo in a 3-way crossover design in healthy participants.
  - Part B evaluated a single dose level (2 mg) of Staccato® alprazolam vs Staccato® placebo in a 2-arm, parallel-group design in participants diagnosed with mild asthma ≥6 months and on a stable asthma drug regimen* for ≥4 weeks before screening.
- The Safety Set (SS) comprised all participants who received ≥1 dose of Staccato® placebo or Staccato® alprazolam.
- The Full Analysis Set (FAS) comprised all participants who were randomised, received ≥1 dose of Staccato® placebo or Staccato® alprazolam, and had a valid day 1 baseline spirometry assessment and ≥1 valid post-baseline spirometry assessment.
- Baseline was defined as the pre-dose value on day 1 or day 4 for post-dose assessments on the respective day.

*As-needed SABAs (short-acting $beta_2$-agonist) or combination low dose ICS-formoterol (inhaled corticosteroid) and/or maintenance treatment with daily low dose ICS or daily LTRA (leukotriene receptor antagonist).

ENDPOINTS (PARTS A AND B)

- Primary safety endpoints were spirometric assessments of changes from baseline in forced expiratory volume in 1 second (FEV_1) analyzed by repeated measures analysis of covariance (ANCOVA) and the incidence of respiratory treatment-emergent adverse events (TEAEs).
- Secondary safety endpoints were the change from baseline in forced vital capacity (FVC), change from baseline in FEV_1/FVC, and the incidence of TEAEs.

Results

PARTICIPANT DISPOSITION AND BASELINE DEMOGRAPHICS

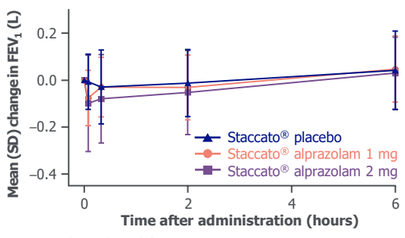
- In Part A, 30 participants were enrolled and randomised to 1 of 6 treatment sequences (1:1:1:1:1:1 ratio) with Staccato® alprazolam 1 mg and 2 mg and Staccato® placebo.
  - Two (6.7%) participants discontinued: 1 participant met a respiratory stopping criterion following administration of the first dose of Staccato® alprazolam 2 mg, and 1 participant withdrew consent after receiving 2 doses of Staccato® alprazolam 1 mg.
- In Part B, 48 participants were randomised; 25 participants received Staccato® placebo and 23 received Staccato® alprazolam 2 mg.
  - One (2.1%) participant in the Staccato® alprazolam 2 mg group met 2 respiratory stopping criteria and discontinued the trial.

Baseline demographics (SS)

	PART A: HEALTHY PARTICIPANTS	PART B: PARTICIPANTS WITH MILD ASTHMA	
	ALL PARTICIPANTS (N=30)	STACCATO® PLACEBO (n=25)	STACCATO® ALPRAZOLAM 2 mg (n=23)
Age, mean (SD), years	30.7 (9.7)	32.2 (8.3)	34.5 (8.8)
Female, n (%)	17 (56.7)	19 (76.0)	10 (43.5)
Racial group, n (%)			
White	21 (70.0)	13 (52.0)	12 (52.2)
Black	3 (10.0)	9 (36.0)	9 (39.1)
Asian	3 (10.0)	2 (8.0)	1 (4.3)
American Indian/ Alaskan Native	1 (3.3)	0	1 (4.3)
Other/mixed	2 (6.7)	1 (4.0)	0

SAFETY: FEV_1, FVC, AND FEV_1/FVC IN HEALTHY PARTICIPANTS (PART A, DAY 1; FAS)

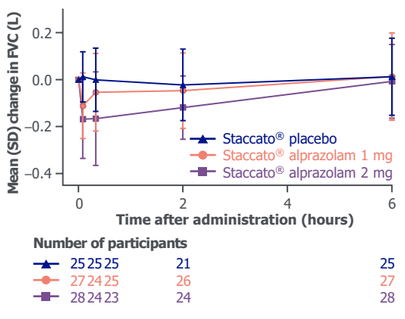
Mean change from baseline in FEV_1



- On day 1, mean change from baseline in FEV_1 showed a greater decrease with Staccato® alprazolam 1 mg (–0.076 L vs –0.007 L) and 2 mg (–0.099 L vs –0.007 L) vs placebo at 5 minutes post-dose, and with Staccato® alprazolam 2 mg vs placebo (–0.080 L vs –0.029 L) at 20 minutes post-dose. These differences vs placebo were statistically significant but not considered clinically relevant.
- Mean FEV_1 values then returned to baseline and were similar across treatment groups.

Changes from baseline were recorded at 5 minutes, 20 minutes, 2 hours, and 6 hours. N values at each time point indicate the number of participants for whom data were collected at that time point and at baseline. Mean (SD) baseline FEV_1 values for Staccato® placebo, Staccato® alprazolam 1 mg, and Staccato® alprazolam 2 mg were 3.461 (0.741) L, 3.466 (0.775) L, and 3.447 (0.716) L, respectively. FEV_1, forced expiratory volume in 1 second.

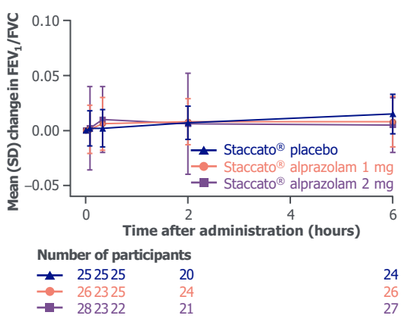
Mean change from baseline in FVC



- On day 1, mean FVC values decreased from baseline at 5 minutes post-dose with Staccato® alprazolam 1 mg, and up to 2 hours post-dose with Staccato® alprazolam 2 mg. These differences vs placebo were statistically significant but not considered clinically relevant.
- Mean FVC values then returned nearly to baseline and were similar across treatment groups.

Changes from baseline were recorded at 5 minutes, 20 minutes, 2 hours, and 6 hours. N values at each time point indicate the number of participants for whom data were collected at that time point and at baseline. Mean (SD) baseline FVC values for Staccato® placebo, Staccato® alprazolam 1 mg, and Staccato® alprazolam 2 mg were 4.184 (0.923) L, 4.292 (1.078) L, and 4.275 (1.039) L, respectively. FVC, forced vital capacity.

Mean change from baseline in FEV_1/FVC

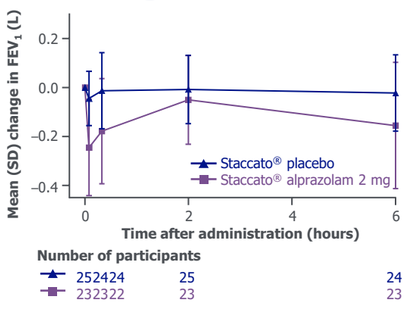


- On day 1, no major changes in FEV_1/FVC were observed after any study treatment.
- No statistically significant differences in FEV_1/FVC change from baseline were observed between study treatments.

Changes from baseline were recorded at 5 minutes, 20 minutes, 2 hours, and 6 hours. N values at each time point indicate the number of participants for whom data were collected at that time point and at baseline. Mean (SD) baseline FEV_1/FVC values for Staccato® placebo, Staccato® alprazolam 1 mg, and Staccato® alprazolam 2 mg were 0.813 (0.061), 0.820 (0.054), and 0.814 (0.058), respectively. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

SAFETY: FEV_1, FVC, AND FEV_1/FVC IN PARTICIPANTS WITH MILD ASTHMA (PART B, DAY 1; FAS)

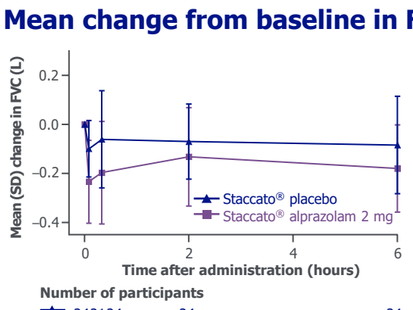
Mean change from baseline in FEV_1



- On day 1, mean change from baseline in FEV_1 values showed a greater decrease with Staccato® alprazolam 2 mg vs placebo at 5 minutes (–0.245 L vs –0.045 L) and 20 minutes (–0.178 L vs –0.013 L) post-dose. These differences vs placebo were statistically significant but not considered clinically relevant.
- Mean FEV_1 returned to values ≥98% of baseline after 20 minutes post-dose except for at 6 hours, likely due to 1 participant with spontaneous bronchospasm-like symptoms (not considered treatment related).

Changes from baseline were recorded at 5 minutes, 20 minutes, 2 hours, and 6 hours. N values at each time point indicate the number of participants for whom data were collected at that time point and at baseline. Mean (SD) baseline FEV_1 values for Staccato® placebo and Staccato® alprazolam 2 mg were 3.057 (0.616) L and 3.374 (0.505) L, respectively. FEV_1, forced expiratory volume in 1 second.

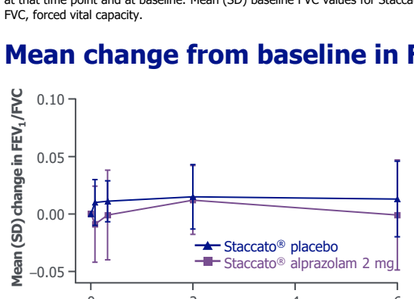
Mean change from baseline in FVC



- On day 1, mean FVC values decreased from baseline with Staccato® alprazolam 2 mg and placebo at all time points.
- Decreases from baseline in mean FVC values were more pronounced with Staccato® alprazolam 2 mg than placebo at 5 and 20 minutes post-dose, and were similar in both treatment groups at 2 and 6 hours.
- These differences vs placebo were statistically significant at 5 and 20 minutes, and at 6 hours post-dose, but were not considered clinically relevant.

Changes from baseline were recorded at 5 minutes, 20 minutes, 2 hours, and 6 hours. N values at each time point indicate the number of participants for whom data were collected at that time point and at baseline. Mean (SD) baseline FVC values for Staccato® placebo and Staccato® alprazolam 2 mg were 4.108 (0.924) L and 4.436 (0.774) L, respectively. FVC, forced vital capacity.

Mean change from baseline in FEV_1/FVC



- On day 1, no major changes in FEV_1/FVC were observed after treatment with either Staccato® placebo or Staccato® alprazolam 2 mg.
- A statistically significant negative difference vs placebo in FEV_1/FVC change from baseline was observed at 5 minutes post-dose; no statistical differences were observed at the other time points.

Changes from baseline were recorded at 5 minutes, 20 minutes, 2 hours, and 6 hours. N values at each time point indicate the number of participants for whom data were collected at that time point and at baseline. Mean (SD) baseline FEV_1/FVC values for Staccato® placebo and Staccato® alprazolam 2 mg were 0.754 (0.079) and 0.770 (0.079), respectively. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Day 4 assessments

- In Part A on day 4, mean changes in FEV_1 from baseline were less marked compared with day 1 and were similar across groups; no statistically significant negative differences in FEV_1 change from baseline were observed after Staccato® alprazolam administration (1 mg or 2 mg dose) compared with Staccato® placebo.
- In Part B on day 4, mean decreases in FEV_1 were less marked than on day 1; no statistically significant negative differences in FEV_1 change from baseline were observed after administration of Staccato® alprazolam 2 mg at any time points.
- For both Parts A and B, changes in FVC and FEV_1/FVC on day 4 were generally similar to day 1, and any statistical differences were not considered clinically relevant.

TOLERABILITY

Incidence of TEAEs (SS)

n (%)	PART A: HEALTHY PARTICIPANTS – DAY 1 STACCATO® PLACEBO (n=28)	DAY 1 STACCATO® ALPRAZOLAM 1 mg (n=29)	DAY 1 STACCATO® ALPRAZOLAM 2 mg (n=29)	DAY 4 STACCATO® PLACEBO (n=28)	DAY 4 STACCATO® ALPRAZOLAM 1 mg (n=29)	DAY 4 STACCATO® ALPRAZOLAM 2 mg (n=28)
Any TEAEs	2 (7.1)	15 (51.7)	26 (89.7)	1 (3.6)	15 (51.7)	24 (85.7)
Drug-related TEAEs	1 (3.6)	15 (51.7)	26 (89.7)	0	15 (51.7)	24 (85.7)
Severe TEAEs[a]	0	0	1 (3.4)	0	0	1 (3.6)
Discontinuation due to TEAEs	0	0	0	0	0	0
Respiratory TEAEs	0	8 (27.6)	12 (41.4)	0	8 (27.6)	9 (32.1)
Drug-related respiratory TEAEs	0	8 (27.6)	12 (41.4)	0	8 (27.6)	9 (32.1)
TEAEs[b] occurring in ≥10% of participants in any group in Part A and B						
Somnolence	1 (3.6)	8 (27.6)	17 (58.6)	0	8 (27.6)	15 (53.6)
Cough	0	8 (27.6)	12 (41.4)	0	8 (27.6)	9 (32.1)
Dizziness	0	0	2 (6.9)	0	0	1 (3.6)
Taste disorder	0	1 (3.4)	0	0	1 (3.4)	0
Sedation	0	3 (10.3)	3 (10.3)	0	1 (3.4)	3 (10.7)

n (%)	PART B: PARTICIPANTS WITH MILD ASTHMA – DAY 1 STACCATO® PLACEBO (n=25)	DAY 1 STACCATO® ALPRAZOLAM 2 mg (n=23)	DAY 4 STACCATO® PLACEBO (n=25)	DAY 4 STACCATO® ALPRAZOLAM 2 mg (n=22)
Any TEAEs	4 (16.0)	23 (100.0)	3 (12.0)	22 (100.0)
Drug-related TEAEs	2 (8.0)	23 (100.0)	1 (4.0)	22 (100.0)
Severe TEAEs[a]	0	3 (13.0)	0	1 (4.5)
Discontinuation due to TEAEs	0	1 (4.3)[c]	0	0
Respiratory TEAEs	0	16 (69.6)	0	15 (68.2)
Drug-related respiratory TEAEs	0	16 (69.6)	0	15 (68.2)
TEAEs[b] occurring in ≥10% of participants in any group in Part A and B				
Somnolence	1 (4.0)	20 (87.0)	0	17 (77.3)
Cough	0	16 (69.6)	0	15 (68.2)
Dizziness	0	4 (17.4)	0	3 (13.6)
Taste disorder	0	4 (17.4)	0	1 (4.5)
Sedation	0	0	0	0

[a]For both Parts A and B on days 1 and 4, all reported incidences of severe TEAEs were non-respiratory (somnolence); [b]Preferred term (Medical Dictionary for Regulatory Activities, Version 24.0); [c]One participant in the Staccato® alprazolam 2 mg dose group discontinued from the trial due to a TEAE of bronchospasm. This event was considered unrelated to the study drug by the investigator and instead reflected the intrinsic variability of the participant's asthma. TEAE, treatment-emergent adverse event.

- In Part A, respiratory TEAEs (all cough) were reported by 8/29 and 12/29 participants on Staccato® alprazolam 1 mg and 2 mg, respectively, on day 1, and by 8/29 and 9/28 participants on day 4.
- In Part B, respiratory TEAEs were reported by 16/23 participants on Staccato® alprazolam 2 mg on day 1 (cough: 16; bronchospasm: 1; dyspnea: 1; dysphonia: 1; throat irritation: 1), and by 15/22 participants on day 4 (cough: 15; throat irritation: 1); the TEAEs of bronchospasm and dyspnea were not considered drug-related by the investigator.
- No respiratory TEAEs occurred with placebo.

Conclusions

- Two doses of Staccato® alprazolam (either 1 mg or 2 mg) administered 72 hours apart were well tolerated in healthy participants and those with mild asthma.
- On day 1, minor decreases in FEV_1 from baseline were observed with Staccato® alprazolam vs placebo at several time points; however, these were not considered clinically relevant.
  - On day 4, decreases in FEV_1 were less marked and were not statistically significant, indicating that there was no increased risk upon repeated dosing.
- No evidence of clinically relevant airway obstruction related to Staccato® alprazolam was observed in healthy participants or those with mild asthma.
- Most TEAEs were mild or moderate in intensity and cough was the most common respiratory TEAE.

References

1. French J, et al. *Epilepsia* 2022;64(2):374-385.

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Phone: +32 2 559 92 00

Email: UCBCares@ucb.com

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