

RESEARCH ARTICLE

Pharmacokinetics and tolerability of single-dose Staccato® alprazolam in adolescents with epilepsy, and population pharmacokinetic analysis to support dose selection in adolescents

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Abstract

Objective: Staccato® alprazolam is a hand-held inhalation device that provides rapid systemic delivery of alprazolam through the intrapulmonary route. This trial explored the pharmacokinetics and tolerability of single-dose Staccato alprazolam 2 mg in adolescents with epilepsy. Pharmacokinetic data were included in a population pharmacokinetic analysis to support adolescent dose selection in the Phase 3 trials.

Methods: Multicenter, Phase 1, open-label trial in adolescents (12–17 years) with focal, generalized, or focal and generalized epilepsy (UP0100/NCT04857307). A single dose of Staccato alprazolam 2 mg was administered in the morning following overnight fast. Pharmacokinetic data were used to update an existing

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population pharmacokinetic model in adults, which was used to investigate dosing in adolescents with epilepsy.

Results: Fourteen patients (6 weighing <50 kg, 8 weighing ≥50 kg) were enrolled and administered Staccato alprazolam 2 mg. Individual plasma alprazolam concentration–time profiles indicated generally rapid absorption (median time to maximum plasma concentration [$C_{\max}$]: 10.5 [range: 2–120] min) with linear elimination. Geometric mean $C_{\max}$, area under the plasma concentration–time curve (AUC) from time 0 to last quantifiable concentration (AUC_{0-t}), AUC from time 0 to infinity ($AUC_{\inf}$), and apparent total body clearance (CL/F) were similar across body weight groups (<50 kg, ≥50 kg). Three patients in the ≥50 kg group reported treatment-emergent adverse events (TEAEs), including dysgeusia, somnolence, dizziness, cough, and hiccups. No severe or serious TEAEs were reported. Simulations of exposure estimates using the updated population pharmacokinetic model indicated similar exposure ($AUC_{\inf}$) for adolescents administered Staccato alprazolam 2 mg compared with the adult reference range, with a slight increase in $C_{\max}$ at lower body weight.

Significance: Alprazolam was rapidly absorbed in most adolescent patients with epilepsy following administration with the Staccato device. No clinically relevant differences between body weight groups were observed on primary pharmacokinetic or safety outcomes. Staccato alprazolam 2 mg was well tolerated. Overall, the present data support the use of Staccato alprazolam 2 mg in adolescents with epilepsy (12–17 years of age).

KEYWORDS

antiseizure medication, inhaled alprazolam, lung delivery, prolonged seizures, Rapid and Early Seizure Termination

1 | INTRODUCTION

Recently, several acute seizure prevention medications with a user friendly delivery mode have been developed for the treatment of acute repetitive seizures (seizure clusters).^{1,2} Acute repetitive seizures are associated with a potential risk of serious consequences, such as status epilepticus, emergency room visits, hospitalizations, and injuries.^{3,4} Acute seizure prevention medications can prevent the next seizure in a cluster of seizures.⁵ However, there are at present no medications that can provide Rapid and Early Seizure Termination (REST) in the outpatient setting. Alprazolam is a commonly used benzodiazepine with demonstrated antiseizure activity.^{6,7} Its antiseizure action is mediated through positive modulation of multiple inhibitory γ -aminobutyric acid (GABA) A receptor subtypes.^{6,7} Alprazolam is primarily metabolized in humans by cytochrome P450 3A4 (CYP3A4).⁸ Concomitant use of strong CYP3A4 inducers (such as carbamazepine, phenobarbital, phenytoin, and primidone) can increase alprazolam metabolism

Key points

- Phase 1 trial evaluating pharmacokinetics, safety, and tolerability of single-dose Staccato alprazolam 2 mg in adolescents with epilepsy.
- Alprazolam concentration–time profiles indicated generally very rapid absorption, followed by linear elimination over time.
- There were no clinically relevant differences in pharmacokinetics between the two adolescent body weight groups (<50 kg and ≥50 kg).
- Lower body weight (<50 kg) did not appear to increase the risk of clinically relevant treatment-emergent adverse events, sedation, or other safety observations.
- The present Phase 1 trial and population pharmacokinetic analysis support the use of Staccato alprazolam 2 mg in adolescent patients 12–17 years of age.

and as a result can decrease plasma levels of alprazolam, potentially reducing efficacy.⁸

Staccato[®] alprazolam is a hand-held inhalation device that provides rapid systemic delivery of alprazolam through the intrapulmonary route.⁹ Staccato alprazolam is under investigation for the rapid termination of stereotypical prolonged seizures.¹⁰ A Phase 1 pharmacokinetic (PK) study showed that alprazolam was rapidly absorbed when administered with the Staccato device, with a time to peak drug plasma concentration achieved within 2 min post-dose in most participants.⁹ Results from a Phase 2a study showed that Staccato alprazolam rapidly suppressed epileptiform activity within 2 min in patients with photosensitive epilepsy, and a Phase 2b study showed that Staccato alprazolam 1 mg or 2 mg can lead to rapid termination of epileptic seizure activity within 2 min of administration.^{6,7}

The Staccato device is breath-actuated, with no priming, coordination between device actuation and breath, or forceful inhalation required by the patient. Only a single, normal breath through the mouthpiece of the Staccato device is needed for device actuation, which enables drug delivery to the deep lung where it is rapidly absorbed at the alveolar-capillary interface. Age-related differences in lung function could potentially affect pulmonary drug delivery.¹¹ It is therefore important to consider developmental lung changes in different age groups for delivery of drugs through the intrapulmonary route. Body weight also varies greatly during adolescence and could affect drug disposition (clearance and distribution).¹²

The present trial evaluated PK and tolerability in a Phase 1, open-label, single-dose trial of Staccato alprazolam in adolescents with epilepsy. Herein we report results from this trial together with a population PK analysis undertaken to support adolescent dose selection in the Phase 3 trials of Staccato alprazolam (EP0162, ClinicalTrials.gov: NCT05077904; EP0165, ClinicalTrials.gov: NCT05076617). In the present trial, safety and tolerability assessments included the incidents of treatment-emergent adverse events (TEAEs), which were any untoward medical occurrence in a patient temporally associated with the use of trial drug, whether or not considered drug related. Sedation and sleepiness were assessed using patients' visual analog scale (VAS) scores.⁶

The objectives of the Phase 1 trial were to evaluate the PK, safety, tolerability, and potential for sedation and sleepiness of Staccato alprazolam 2 mg in adolescents with epilepsy following a single inhaled dose. The objectives of the population PK analysis were to update an existing population PK model in adult patients with data from adolescent patients in this Phase 1 trial, and to use the updated population PK model to simulate dosing in adolescent patients to evaluate the need for potentially updated dosing recommendations in adolescents (12–17 years) with epilepsy.

2 | METHODS

2.1 | The adolescent trial (UP0100)

2.1.1 | Trial design

The adolescent trial (UP0100, ClinicalTrials.gov: NCT04857307) was a multicenter, Phase 1, open-label, nonrandomized, single-dose trial in adolescents aged 12–17 years with focal, generalized, or focal and generalized epilepsy, conducted in the United States. The trial protocol, amendments, and participant informed consent were reviewed by national, regional, or local institutional review boards. The trial was conducted in accordance with the applicable regulatory and International Council for Harmonisation-Good Clinical Practice requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

The trial consisted of a screening period of up to 28 days, a 2-day treatment period, and a 7-day safety follow-up period (± 2 days). A single dose of Staccato alprazolam 2 mg was administered in the morning following an overnight fast of ≥ 10 h. Serial blood samples were collected pre-dose and at 2, 10, and 30 min and 1, 2, 6, 24, and 36 h post-dose for alprazolam plasma PK evaluation by noncompartmental analysis.

2.1.2 | Patient eligibility

Patients were eligible to enroll in the trial if they were male or female with a body weight of ≥ 29 kg, a body mass index of $14\text{--}32\text{ kg/m}^2$, had forced expiratory volume in 1 s and forced vital capacity $>80\%$ of predicted at screening, were nonsmokers for ≥ 6 months before screening and had never smoked >5 cigarettes in a day, and were taking ≥ 1 concomitant antiseizure medications (ASMs). Patients treated concomitantly with strong CYP3A4 inducers were excluded.

The study stipulated enrollment of at least six patients with body weight <50 kg in order to evaluate the potential impact of low body weight on PK and safety. The first set of patients assessed ($n=6$, including ≥ 2 adolescents with body weight <50 kg) were dosed at 2 mg. Once the PK and safety data from the first six patients were reviewed by the Safety Monitoring Committee, the second set ($n=8$) of patients was also dosed at 2 mg.

2.1.3 | Outcomes and statistical analysis

Plasma PK was evaluated by noncompartmental analysis. Primary PK endpoints were maximum plasma

concentration ($C_{\max}$), area under the plasma concentration–time curve (AUC) from time 0 to last quantifiable concentration (AUC_{0-t}), AUC from time 0 to infinity (AUC_{∞}), and apparent total body clearance (CL/F). Other PK endpoints included time to $C_{\max}$ ($T_{\max}$), apparent volume of distribution (V_{ss}/F), and plasma elimination half-life ($t_{1/2}$). Blood samples were collected for measurement of blood concentrations of alprazolam on Day 1 of the treatment period, pre-dose, and then following administration of study drug at 2, 10, and 30 min, and 1, 2, 6, 24, and 36 h post-dose. Standard noncompartmental analysis was applied on the drug plasma concentration–time data. Actual blood sampling times were used for deriving the PK parameters.

Primary safety endpoints were the incidents of TEAEs and serious TEAEs. Other safety endpoints included assessment of level of sedation and sleepiness using a sedation VAS and sleepiness VAS (subjective assessments). VAS assessments were performed pre-dose, and at 2, 10 and 30 min and 1, 2, 6, 24, and 36 h post-dose (the 12-h time point was originally included but later removed after a protocol amendment). A sensitivity analysis was conducted to exclude the VAS results of one patient who was asleep at the baseline VAS assessment, precluding evaluation of increase in sedation or sleepiness after treatment.

Statistical analysis was conducted using SAS® version 9.4. The PK noncompartmental analysis was performed using Phoenix WinNonlin® version 8.3.

2.1.4 | Bioanalytical method

For the quantification of alprazolam in human plasma containing sodium heparin, a liquid chromatography tandem mass spectrometry method employing electrospray ionization was developed and validated, according to the US Food and Drug Administration (FDA) Guidance for Industry (Bioanalytical Method Validation, May 2018). Liquid–liquid extraction was used for sample preparation, and the analysis was conducted with gradient elution on a C18 reversed-phase column. The method was validated for alprazolam over the nominal range of 0.200–40.0 ng/mL.

2.2 | Population PK analysis

PK data were used to update an existing (unpublished) population PK model in adult patients. PK data of Staccato alprazolam from the following three trials were used in the modeling: the Phase 2a, randomized, double-blind, crossover trial of Staccato alprazolam 0.5, 1, and 2 mg and Staccato placebo in adult patients with photosensitive epilepsy (AMDC-002-202, ClinicalTrials.gov: NCT02351115;

$N=5$)⁷; the Phase 2b, open-label feasibility and double-blind, randomized, parallel group, dose-ranging trial of Staccato alprazolam 1 and 2 mg and Staccato placebo in adult patients with epilepsy (ENGAGE-E-001, ClinicalTrials.gov: NCT03478982; $N=84$)⁶; and adolescent data from the UP0100 trial presented here (ClinicalTrials.gov: NCT04857307; $N=14$).

The population PK model incorporated two absorption processes consisting of immediate release into the central compartment and first-order absorption from an absorption compartment, where the relative contribution of the two processes was estimated for each individual patient profile, together summing to 100%. Absorption was followed by distribution to a central compartment and a peripheral compartment, and linear elimination from the central compartment.

In the final population PK model, no relationship between body weight and clearance (CL) or intercompartmental clearance (Q) could be detected. Allometric scaling of CL and Q was therefore not implemented, whereas freely estimated allometric scaling coefficients were included for central volume (V_c) and peripheral volume (V_p). Stepwise covariate modeling was performed for covariate effects on CL and V_c , and simulations were performed to investigate exposure measures for adolescents. Covariates at baseline considered in the analysis included height, sex, age, concomitant ASMs, benzodiazepine use, creatinine clearance, and alanine aminotransferase (Table S1).

The National Health and Nutrition Examination Survey Dual-Energy X-ray Absorptiometry (NHANES DXA) database was used to provide demographic variables of age (≥ 12 years) and body weight for adults and adolescents simulated with and without the co-administration of strong hepatic enzyme-inducing ASMs (carbamazepine, phenobarbital, phenytoin, and primidone). Alprazolam PK parameters were sampled using the updated adult/adolescent population PK model NONMEM estimates and were combined with the body weights from the NHANES database to arrive at sampled individual PK parameters (see the Supplementary Methods for further details).

The population analysis was performed using the nonlinear mixed-effects modeling software NONMEM version 7.5.0, supplemented with Perl-speaks-NONMEM (PsN, version 5.3.0). R software version 4.0.5 was used for data management, simulation using the RxODE package, evaluation of goodness of fit, and model evaluation. The adequacy of the model was evaluated using simulation-based visual predictive check methods (Supplementary Methods; Figure S1).^{13,14} Parameter estimation was performed in NONMEM using first-order conditional estimation with the INTERACTION option.

3 | RESULTS

3.1 | The adolescent trial (UP0100)

3.1.1 | Demographics, disposition, and baseline characteristics

The adolescent trial was conducted between April 2021 and April 2022 in the United States. Of 17 patients who were screened, 14 entered the treatment period (6 weighing <50 kg, 8 weighing ≥50 kg) and received a single dose of Staccato alprazolam 2 mg. All 14 patients completed the study and were included in both the Safety Set and PK Set. Most patients (12/14) were female, mean age was 15.1 years (range: 12–17 years), and mean body weight was 54.46 kg (range: 33.5–81.2 kg) (Table S2). All patients had prior and concomitant ASMs, including lamotrigine and oxcarbazepine (4 [28.6%] each); levetiracetam (3 [21.4%]); clonazepam, midazolam, zonisamide (2 [14.3%] each); and brivaracetam, clobazam, felbamate, topiramate, and valproic acid (1 [7.1%] each). Clonazepam and midazolam were used on an as-needed

basis in two patients each, and neither was used on a daily basis by any patients. The most recent administration of clonazepam or midazolam was 193 days before alprazolam administration.

3.1.2 | Pharmacokinetics

Following administration of Staccato alprazolam 2 mg, alprazolam concentration–time profiles indicated generally rapid absorption (median T_{max} of 10.50 min [range: 2.00–120 min]), followed by linear elimination over time, with a similar PK profile across adolescent body weight groups (Figure 1). The geometric mean plasma concentrations of alprazolam at 2 min post-dose were 31.76 ng/mL (range of error bars: 12.79–78.88 ng/mL) in patients <50 kg and 20.31 ng/mL (range of error bars: 7.639–53.99 ng/mL) in patients ≥50 kg (Figure 1). Some patients had a second absorption peak or delayed absorption, and relatively high between-patient variability was observed during both the absorption and elimination phases; however, no obvious outliers were seen in the spaghetti plots (Figures 2

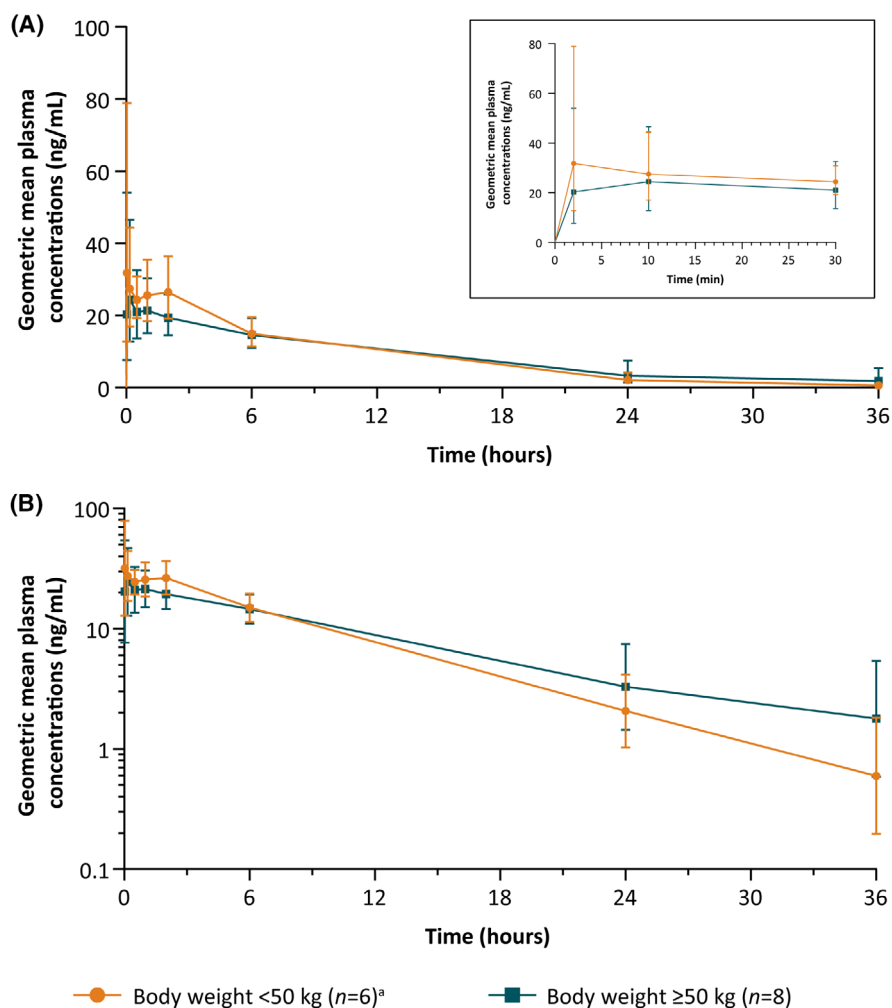


FIGURE 1 Geometric mean plasma alprazolam concentration–time profiles following single-dose administration of Staccato alprazolam 2 mg on (A) linear scale and (B) semilogarithmic scale. Lower limit of quantification was 0.200 ng/mL. Error bars are geometric mean $\times/\div$ geometric standard deviation.¹⁵
^a $n = 5$ at 2 and 30 min.

and S2). Geometric mean $C_{\max}$, plasma exposure (AUC_{inf} and AUC_{0-t}), and CL/F were similar across body weight groups (Table 1). Shorter geometric mean of terminal $t_{1/2}$ and lower geometric mean V_{ss}/F values were observed for patients in the <50 kg body weight group compared with patients in the ≥ 50 kg body weight group; however, these differences were not considered to be clinically relevant.

3.1.3 | Safety and tolerability

Overall, three patients reported TEAEs, all in the ≥ 50 kg body weight group (Table 2). All reported TEAEs were considered by the investigator to be related to Staccato alprazolam. All TEAEs were mild in intensity, except for

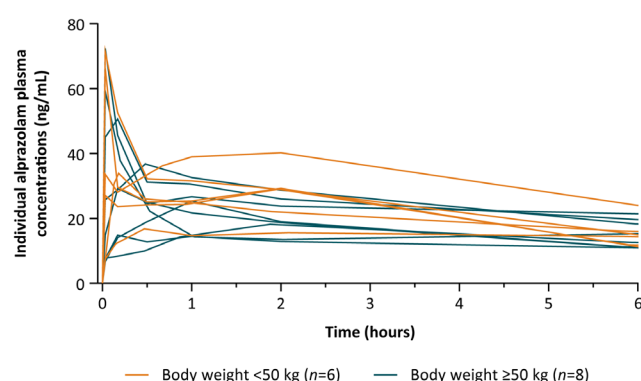


FIGURE 2 Individual plasma alprazolam concentration-time profiles following single-dose administration of Staccato alprazolam 2 mg up to 6 h. Lower limit of quantification was 0.200 ng/mL. The actual assessment times are presented.

two events of somnolence, which were moderate in intensity. No severe or serious TEAEs were reported. There were no respiratory TEAEs indicative of bronchospasm (wheezing or dyspnea). No clinically relevant changes in laboratory parameters, vital signs, or electrocardiography were reported.

After administration of Staccato alprazolam, mean sedation VAS scores decreased very rapidly from baseline (indicating a higher level of sedation). An increase in sedation was already observed at the first time point recorded (2 min post-dose), and maximum effect on alertness was reached within 10 min and lasted for ~1 h. Thereafter, the sedation effect tended to decrease over time and returned close to baseline values by 6 h post-dose (Figures 3 and S3). Mean changes from baseline for sedation followed similar patterns over time for the two body weight groups. The lowest mean change from baseline occurred at 10 min post-dose for the <50 kg body weight group and at 1 h post-dose for the ≥ 50 kg body weight group for sedation. A similar pattern was observed for sleepiness VAS scores (Figures S3 and S4).

3.2 | Population PK analysis

NONMEM parameter estimates for the two-compartment adult/adolescent population PK model are presented in Table S3. The fast absorption fraction was estimated at 0.369 (95% confidence interval [CI]: 0.156–0.649), and the absorption rate constant for the slow absorption component was 5.37 (3.88–7.45) h^{-1} , which translates to an absorption half-life of 7.74

Parameter	Body weight <50 kg (n=6)	Body weight ≥ 50 kg (n=8)	All patients (N=14)
Geometric mean (geometric CV%)			
$C_{\max}$, ng/mL	38.27 (58.3)	33.55 (61.1)	35.50 (57.8)
AUC_{inf} , h.ng/mL	281.1 (26.8)	278.8 (46.4) ^a	280.0 (35.8) ^b
AUC_{0-t} , h.ng/mL	270.8 (26.4)	283.8 (44.4)	278.2 (36.2)
CL/F , L/h	7.114 (26.8)	7.174 (46.4) ^a	7.144 (35.8) ^b
$T_{\max}$, min ^c	19.50 (2.00, 120) ^d	10.00 (2.00, 113) ^d	10.50 (2.00, 120) ^d
V_{ss}/F , L	67.53 (30.8)	87.38 (23.8) ^a	76.82 (29.7) ^b
$t_{1/2}$, h	6.816 (31.2)	8.477 (26.9) ^a	7.601 (30.1) ^b

Abbreviations: AUC_{inf} , area under the plasma concentration–time curve from time 0 to infinity; AUC_{0-t} , area under the plasma concentration–time curve from time 0 to last measurable concentration; CL/F , apparent total body clearance; $C_{\max}$, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; $t_{1/2}$, plasma elimination half-life; $T_{\max}$, time to maximum plasma concentration; V_{ss}/F , apparent volume of distribution.

^an = 6.

^bn = 12.

^cData are median (minimum, maximum).

^dFour of 14 patients (2 in each body weight group) had $T_{\max}$ at 2 min.

TABLE 1 Plasma PK (noncompartmental analysis) of alprazolam following single-dose administration of Staccato alprazolam 2 mg.

TABLE 2 Incidence of TEAEs following single-dose administration of Staccato alprazolam 2 mg.

n (%)	Body weight <50 kg (n = 6)	Body weight ≥50 kg (n = 8)	All patients (N = 14)
Any TEAEs	0	3 (37.5)	3 (21.4)
Serious TEAEs	0	0	0
Severe TEAEs	0	0	0
Drug-related TEAEs	0	3 (37.5)	3 (21.4)
Respiratory TEAEs	0	2 (25.0)	2 (14.3)
TEAEs ^a			
Dysgeusia	0	3 (37.5)	3 (21.4)
Somnolence	0	3 (37.5)	3 (21.4)
Dizziness	0	2 (25.0)	2 (14.3)
Cough	0	2 (25.0)	2 (14.3)
Hiccups	0	2 (25.0)	2 (14.3)

Abbreviation: TEAE, treatment-emergent adverse event.

^aMedical Dictionary for Regulatory Activities version 24.0 Preferred Term.

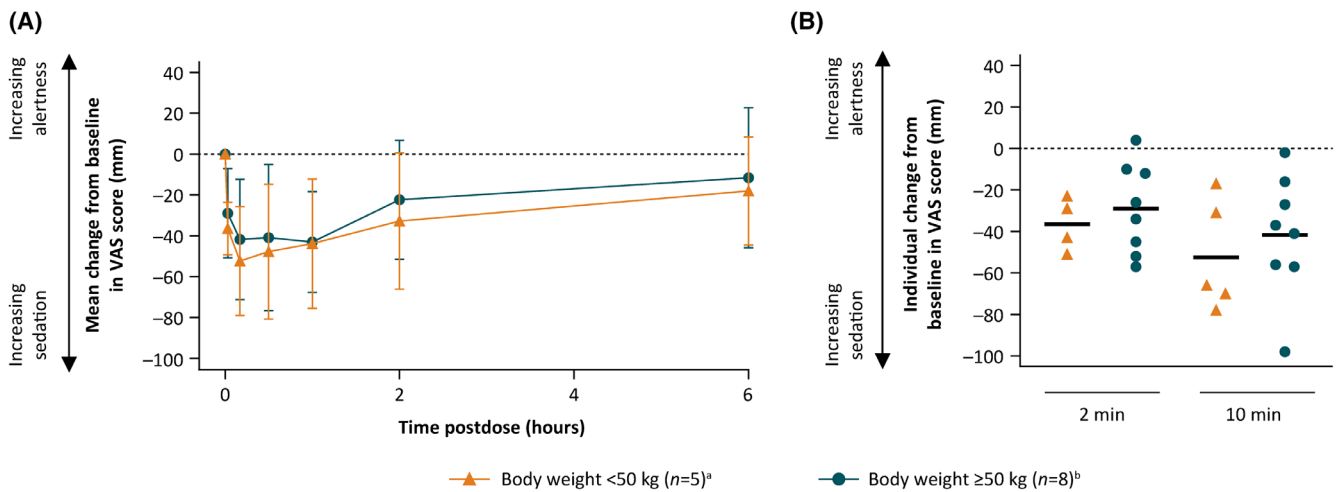


FIGURE 3 Sedated-Alert (0–100 mm) VAS. (A) Mean changes from baseline over time and (B) scatter plots of individual changes from baseline at 2 and 10 min post-dose (black horizontal lines indicate mean change from baseline in VAS score at each time point). Lower VAS scores indicate a higher level of sedation. Error bars are standard deviations. ^an = 4 at 2 and 30 min. ^bn = 7 at 1 h. VAS, visual analog scale.

(5.58–10.7) min. Clearance was 8.23 (7.23–9.38) L/h, and this increased by 95.5% (50.5%–154.0%) in the presence of strong inducer ASMs. The simulated range of AUC_{inf} and C_{max} values in the adolescent body weight and age range closely matched the adult reference range (Figures 4 and S5). There was a slight increase in C_{max} at lower body weight, driven by the body weight scaling on V_c and V_p . Although no inducer ASMs were administered to adolescents, the model predicted lower overall alprazolam exposure (AUC_{inf}) with co-administration of inducer ASMs, but no change in C_{max} . Assessment of age as a covariate demonstrated that the fold change in alprazolam clearance across 95% of the observed age range (with 95% CI) was estimated to be 1.40 (0.944–2.09), suggesting no significant relationship between age and alprazolam clearance.

4 | DISCUSSION

The results from the adolescent trial show that, following administration with the Staccato device, alprazolam was rapidly absorbed in most adolescent patients with epilepsy and demonstrated linear plasma elimination. C_{max} was reached rapidly in most patients (with a median T_{max} of 10.5 min). Variability in T_{max} was observed during the absorption phase. This variability in absorption is similar to that observed in previous studies of Staccato alprazolam in adult healthy volunteers,⁹ and with other drugs using inhalation as the route of administration.^{16,17} Some patients had a slower absorption component with a second peak plasma concentration, also suggesting some variability in absorption. Although particle size distribution from the Staccato device optimally targets deep lung delivery to enable very

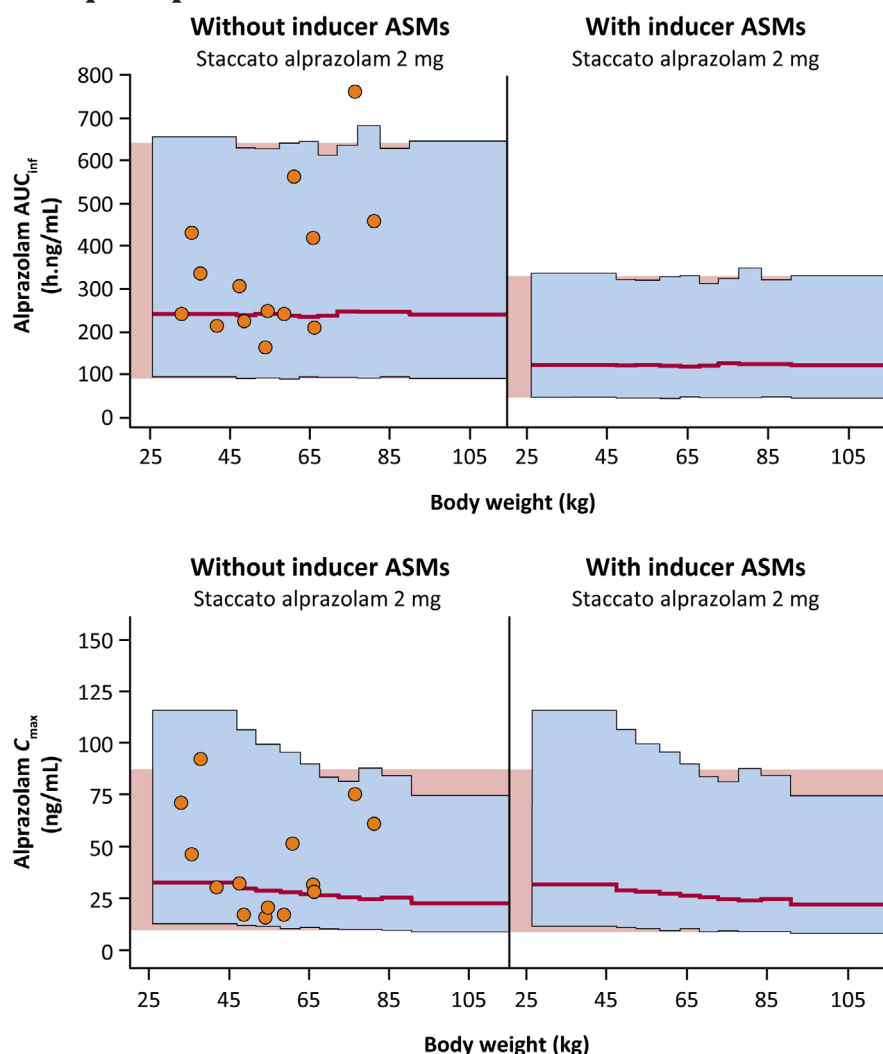


FIGURE 4 Simulated distribution of PK parameters of Staccato alprazolam 2 mg by body weight in adolescents using the population PK model. The x-axis is restricted to 115 kg. Red line and blue area: median and 90% of simulated alprazolam values for adolescent samples from the NHANES database. Orange dots: individual predicted alprazolam values for adolescents in the UP0100 clinical trial. The horizontal pink bar is the simulated 90% range of values in adults receiving the Staccato alprazolam 2 mg dose. Adolescents in the UP0100 clinical trial did not receive inducer ASMs; however, the model can predict the exposures based on the adult data. ASM, antiepileptic medication; AUC_{inf} , area under the plasma concentration–time curve from time 0 to infinity; C_{max} , maximum plasma concentration; PK, pharmacokinetic.

fast absorption, partial drug deposition may additionally occur in the upper and lower bronchial airways—resulting in a slower absorption rate—and in the oral mucosa. In addition, it is possible that the drug can be swallowed and absorbed through the gastrointestinal tract.^{18,19} Given the known variability in drug deposition and the multiple and complex processes leading to drug absorption following inhalation, some degree of variability is expected to be observed in the absorption phase. However, despite the observed variability in T_{max} , it is important to note that effective alprazolam plasma levels are already achieved within 2 min post-dose as suggested by the decreases in sedation and sleepiness VAS scores (indicating increases in sedation and sleepiness, respectively) from baseline by 2 min post-dose. These data demonstrate that the effect of Staccato alprazolam is not driven by C_{max} or T_{max} but rather by the alprazolam plasma concentration achieved quickly after administration (within 2 min post-dose).

The updated population PK model containing data from patients (adults and adolescents) with epilepsy was shown to adequately describe the observed alprazolam

concentration profiles, allowing the model to be used for simulations. Based on visual inspection of the graphs, the PK model illustrates that although an increase in C_{max} may be detected at the low extreme of the adolescent weight and age distributions, most values fall within the adult reference range. The modeling results therefore suggest that Staccato alprazolam 2 mg provides alprazolam exposure in adolescents that is similar to the exposure in adults. No adolescents in the current Phase 1 trial were co-administered with inducer ASMs; however, the simulated ranges illustrate their effect, nonetheless.

Within the adolescent population, body weight can vary significantly. In the adolescent trial, body weight ranged from 33.5 kg to 81.2 kg and had no clinically relevant effect on the PK in adolescents. There were no notable differences in the plasma noncompartmental PK of alprazolam for C_{max} , AUC_{inf} , AUC_{0-t} , and CL/F values between the two body weight groups. Numerical differences in the geometric mean V_{ss}/F values (<50 kg: 67.53 L; ≥50 kg: 87.38 L) and $t_{1/2}$ values (<50 kg: 6.816 h; ≥50 kg: 8.477 h) between the two body weight groups were not considered to be clinically

relevant. In the population PK analysis, the effect of body weight on V_c and V_p resulted in a slight increase in C_{max} and early exposure values for lower body weight adolescents. Exposure estimates from simulations indicated similar exposure (AUC_{inf}) for adolescents administered Staccato alprazolam 2mg compared with the adult reference range, which can be expected in the absence of a relationship between body weight and alprazolam clearance (as was the case in the final population PK model).

In the PK modeling study, the absence of a relationship between age and alprazolam clearance was as expected based on the known developmental changes for the CYP3A4 enzyme, the main enzyme involved in alprazolam metabolism.⁸ In the adolescent age group that we evaluated (12–17years), maturation of CYP enzymes is complete, and metabolic activities are similar to those observed in adults.^{20–22} In addition, based on the known maturation of CYP enzymes, we do not expect the enzyme-inducing effects of other ASMs on alprazolam to be different between adults and adolescents. Similarly, the present data do not provide evidence of a major effect of age on lung absorption as expected considering that lung function increases linearly with height and age until the adolescent growth spurt (around 12years of age in males and 10years in females).¹¹ Overall, results from the adolescent trial and PK modeling study are aligned with a study of extended release oral alprazolam (1 mg and 3 mg), which showed that the PK of alprazolam is similar in adolescents and adults.²³

Single-dose administration of Staccato alprazolam 2mg was generally well tolerated in adolescents with epilepsy, and no new safety signals were identified in the adolescents. A numerically higher incidence of TEAEs was reported in patients in the higher body weight group (≥ 50 kg: 37.5%; < 50 kg: 0); however, this may have happened by chance given the low sample size in the trial (eight and six patients in each body weight group, respectively). Increases in sedation and sleepiness were observed immediately after dosing and returned close to baseline values by 6h post-dose. Variability was observed in the sedation VAS results. VAS is a subjective measure and may accordingly vary. Overall, these safety findings were consistent with previous Phase 1 and Phase 2 studies of Staccato alprazolam in adult study participants.^{6,9}

Limitations of the present adolescent trial include the low number of patients with very low body weight (around 30kg) to better characterize the body weight impact, if any; the high proportion of female patients ($n = 12/14$); and the low number of PK samples collected immediately after dosing (2, 10, and 30min during the absorption phase) for an accurate estimation of C_{max} and T_{max} , as these are discrete PK parameters that are dependent on the sampling schedule.

Overall, alprazolam was rapidly absorbed in most adolescent patients with epilepsy following administration with the Staccato device, and no clinically relevant differences in PK parameters between body weight groups (< 50 kg and ≥ 50 kg) were observed. Lower body weight did not appear to increase the risk of clinically relevant TEAEs, sedation, or other safety observations. Overall, the present data support the use of a 2mg dose of Staccato alprazolam in adolescent patients 12–17years of age. The PK profile of inhaled alprazolam suggests it may be a suitable medication for REST in adolescents as well as adults.

AUTHOR CONTRIBUTIONS

Pavel Klein: investigation (equal) and writing – review & editing (equal). **Gewalin Aungaroon:** investigation (equal) and writing – review & editing (equal). **Victor Biton:** investigation (equal) and writing – review & editing (equal). **Kore Kai Liow:** investigation, conceptualization, and formal analysis. **Steven Phillips:** investigation (equal) and writing – review & editing (equal). **Thomas Wychowski:** investigation (equal) and writing – review & editing (equal). **Ahmed Sadek:** investigation (equal) and writing – review & editing (equal). **Jan-Peer Elshoff:** writing – review & editing (equal). **Robert Roebeling:** writing – review & editing (equal). **Aliceson King:** writing – review & editing (equal). **Chiara C. Rospo:** writing – review & editing (equal). **Rik Schoemaker:** methodology for the PK modeling study (lead); formal analysis (equal); and writing – review & editing (equal). **Hugues Chanteux:** conceptualization (lead); supervision (lead); and writing – review & editing (lead).

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This trial and the population PK analysis were funded by UCB, which was responsible for the trial design and collection and analysis of the data. The authors, some of whom are UCB employees, were responsible for data interpretation, revising the manuscript for intellectual content, and approving of the manuscript for submission.

CONFLICT OF INTEREST STATEMENT

Staccato® is a registered trademark of Alexza Pharmaceuticals, Inc., and is used by UCB under license. P. Klein has served as a consultant for Abbott, Arvelle Therapeutics, Neurelis, and SK Life Science; consultant, advisory board member, and speaker for Aquestive Therapeutics, Eisai, Sunovion, and UCB; is a member of the medical advisory board of Stratus and the scientific advisory board of OB Pharmaceuticals; is CEO of PrevEp; and has received research support from CURE, Department of Defense, and Lundbeck. G. Aungaroon has served as an advisory board member for Biocodex; has received research grants from Epigenix Therapeutics, Eysz, Jazz Pharmaceuticals, and UCB; and has received consulting fees from the Epilepsy Study Consortium. V. Biton and T. Wychowski report no disclosures. K.K. Liow received research funding from Engage Therapeutics and UCB. S. Phillips has no conflicts of interest. A. Sadek has served as advisory board member for GW Pharmaceuticals and SK Life Science; speaker for Sunovion; and has received research support from Sunovion and UCB. J.P. Elshoff, R. Roebing, A. King, C.C. Rospo, and H. Chanteux are salaried employees of UCB and receive stock or stock options from their employment. R. Schoemaker is a paid consultant for UCB.

DATA AVAILABILITY STATEMENT

UCB does not share participant-level data for Phase 1 clinical trials or modeling data.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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