Inhaled alprazolam rapidly suppresses epileptic activity in photosensitive participants

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Abstract
Objective: Treatment options for seizure clusters are limited; the need for easy-to-administer treatments remains. The Staccato system delivers drug deep into the lung via inhalation. In this phase 2a study, we investigated the ability of three different doses of Staccato alprazolam to suppress the electroencephalographic (EEG) photoparoxysmal response (PPR) compared with placebo in participants with photosensitive seizures.

Methods: Adults (18-60 years) with a diagnosis and history of PPR on EEG with or without an epilepsy diagnosis were eligible to participate. Participants received Staccato alprazolam 0.5, 1.0, and 2.0 mg, and Staccato placebo (twice) in random order. Intermittent photic stimulation and clinical assessments were performed at one predose and seven postdose time points. The primary endpoint of the study was the change in standardized photosensitivity range (SPR) in participants receiving each dose of Staccato alprazolam.

Results: Fifteen participants with a prior epilepsy diagnosis were screened; five were enrolled, randomized, and completed the study. All participants were white females with a mean (SD) age of 27.2 (6.8) years. All doses of Staccato alprazolam reduced the SPR at 2 minutes; the effect was sustained through 4 hours for the 0.5-mg dose and 6 hours for the 1.0- and 2.0-mg doses. The magnitude and duration of sedation and sleepiness were dose-related. Four participants (80%) experienced ≥1 adverse event (AE); none was severe or serious. Cough, diarrhea, dysgeusia, oral dysesthesia, sedation, and somnolence were experienced by two participants (40%) each.

Significance: This proof-of-concept study demonstrated that Staccato alprazolam 0.5, 1.0, and 2.0 mg rapidly suppressed epileptiform activity in photosensitive participants with epilepsy. The AE profile of Staccato alprazolam was similar to what has been reported for alprazolam for other indications. The results support further development of Staccato alprazolam as a rescue medication for the acute treatment of seizures.
1 | INTRODUCTION

There is a need for acute treatment options for seizure clusters (defined as "acute repetitive seizures"), as well as other seizure emergencies. The only approved therapy for seizure clusters is Diastat, diazepam formulated as a gel that is administered rectally via syringe, which requires the aid of a caregiver, is inconvenient to administer outside of the home, and may be socially embarrassing for some participants. Diastat has been shown to prevent or delay subsequent seizures in an ARS episode, but it does not abort the first seizure. Several drugs in recent development may be superior to rectal diazepam, including buccal midazolam, intranasal midazolam, and intranasal diazepam; however, the pharmacokinetics (PK) of these agents suggests that they would reach an effective serum concentration likely to stop seizures after 5 minutes or more. In addition, there are no currently approved therapies for evolving seizure activity in the absence of an identified cluster. Given that significant seizure activity may occur in the first 10 minutes after seizure or cluster onset is recognized—for example, a cluster of myoclonus preceding a generalized tonic-clonic seizure, a prolonged focal aware seizure preceding impaired awareness or bilateral tonic-clonic seizure—the development of fast-onset treatment options that can be easily administered in the outpatient setting is vital. Alprazolam administered via the Staccato inhalation system is a potential therapy that could rapidly treat evolving seizure activity or seizure clusters.

Alprazolam, an allosteric modulator of multiple γ-aminobutyric acid type A (GABA<sub>A</sub>)-receptor subtypes, is a well-known and highly characterized benzodiazepine for the treatment of anxiety disorders. Treatment of seizures with alprazolam may be appropriate as the antiseizure properties of benzodiazepines are believed to be mediated by actions on GABA<sub>A</sub>-receptor subtypes, and alprazolam is potent and efficacious in various animal models of antiseizure activity. In one comparator study, alprazolam was more potent than either clonazepam or diazepam in reducing audiogenic seizures.

The Staccato system aerosolizes a drug and, via inhalation, delivers it deep into the lung for rapid systemic exposure. The Staccato formulation of alprazolam was initially developed as a rapid treatment option for participants with anxiety. A study in induced panic attack showed that treatment with Staccato alprazolam did not reduce the frequency and duration of panic symptoms compared with placebo; peak plasma concentrations following administration of Staccato alprazolam were achieved following inhalation within minutes, and rapid onset of pharmacodynamic (PD) effects of somnolence and sedation were observed (unpublished data).

Key Points

- The Staccato system delivers drug deep into the lung via inhalation
- We investigated the ability of Staccato alprazolam 0.5, 1.0, and 2.0 mg to suppress the photoparoxysmal response compared with placebo in participants with photosensitive seizures
- Results showed that Staccato alprazolam 0.5, 1.0, and 2.0 mg rapidly suppressed epileptiform activity in photosensitive participants with epilepsy
- The AE profile of Staccato alprazolam was similar to what has been reported for alprazolam for other indications

As seizures occur sporadically and unpredictably, it is difficult to determine the time to PD effect of a novel agent or administration route. Several prior antiepileptic drugs (AEDs) have been developed using participants with a photoparoxysmal response (PPR) on electroencephalogram (EEG) to provide initial data on the drugs' potential antiepileptic activity. Suppression of photic stimulation-induced epileptiform activity in such individuals indicates an anticonvulsive effect of potential AEDs; trials using such participants have been conducted for lamotrigine, levetiracetam, and brivaracetam among others. As epileptic activity can be elicited at will and with precise timing in these participants, eliciting a PPR provides an ideal opportunity to explore time to onset of action of a drug. We therefore used participants with photosensitivity to explore the time to onset of action of inhaled alprazolam using the Staccato system. This trial is a phase 2a study that evaluated the ability of three different doses of Staccato alprazolam to suppress the PPR in participants with and without epilepsy compared with placebo.

2 | MATERIALS AND METHODS

2.1 | Study design

Trial AMDC-002-202 (NCT02351115) was a phase 2a, multicenter, randomized, double-blind, crossover, placebo-controlled study conducted in participants with a known stable PPR on EEG (Figure 1). After the screening visit, participants returned five additional times to receive, in random order, Staccato placebo (two times) and Staccato alprazolam 0.5, 1, and 2 mg. On each study day, intermittent photic stimulation (IPS) and clinical assessments were performed at eight predetermined times over
the course of the day, one predose and seven postdose. Each visit was at least 7 days apart. Study personnel observed the administration of study medication. If possible, each participant’s AED regimen was kept stable over the course of the study. IPS methodology is described in detail in Appendix S1.

2.2 | Participants

Participants eligible to participate in the trial were adults (18-60 years old, inclusive), had a body mass index (BMI) ≥ 18 and ≤ 35 kg/m², had a diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy for which they were receiving 0-2 concomitant AEDs, and had a reproducible IPS-induced PPR on EEG of ≥3 points on a frequency assessment scale in at least one eye condition (ie, eyes open, eyes closed, and eye closure) on at least three of five EEGs performed during the screening visit.

Participants were excluded if they had any of the following: a history of nonepileptic seizures, seizure worsening in response to narrow-spectrum drugs, active central nervous system (CNS) infection, demyelinating disease, degenerative neurological disease or any progressive CNS disease, use of more than two concomitant AEDs for epilepsy treatment, use of known inhibitors or inducers of cytochrome P450, a history within the past year of drug or alcohol dependence or abuse, a current history of asthma, chronic obstructive lung disease, or any lung disease associated with bronchospasm, or use of medications to treat airway disease, or any acute respiratory signs/symptoms (eg, wheezing). Full participant inclusion and exclusion criteria are provided in Appendix S1.

2.3 | Objectives, endpoints, and outcome measures

The objectives of this trial were to assess the effects of Staccato alprazolam on the IPS-induced PPR EEG response in participants with epilepsy and to assess the ability of Staccato alprazolam to suppress epileptic activity at the earliest tested time point (2 minutes). Additional objectives included correlating plasma concentrations of Staccato alprazolam with PD effects on IPS and sedation, to assess the sedative properties of the Staccato alprazolam doses to select maximally effective dose with the least sedation for future clinical studies, and to assess the safety of a single dose of Staccato alprazolam in participants with photosensitive epilepsy.

The primary endpoint of the study was the change in standardized photosensitivity range (SPR) in participants receiving each dose of Staccato alprazolam (described in Appendix S1 in detail). The SPR is defined as the number of IPS frequencies that produce a photoepileptiform response in a given individual. Participants were exposed to IPS at 14 standard frequencies. Flashes at ascending frequencies from 2 Hz were administered until epileptiform activity appeared, defining the lower SPR threshold frequency. This process was repeated descending from 60 Hz to determine the upper threshold frequency. Secondary endpoints included the assessment of sedation and somnolence using two visual analog scales, correlation of plasma concentrations of Staccato alprazolam with PD effects on the SPR, correlation of plasma concentrations of Staccato alprazolam with PD effects on sedation, assessment of adverse events (AEs) and changes in the neurological examination, and time to onset of effect.

Efficacy outcome measures included PD and PK assessments and PPR evaluations. Safety evaluations included AEs, clinical laboratory assessments, and sedation assessments.

2.4 | Statistical analyses

Data were reported using descriptive statistics. Both Staccato placebo administrations were pooled as one treatment. Previous
studies of the PPR typically used small participant numbers in a crossover design. Given that this is a proof-of-concept trial, there is no formal sample size estimate; the number of participants enrolled was based on the limited number of participants who fit the strict PPR reproducibility criteria.

3 | RESULTS

3.1 | Participants

Between January 8, 2015 and July 22, 2016, 15 participants with a previous epilepsy diagnosis were screened and five were enrolled and randomized (Figure 2). Of the 10 screen failures, nine participants failed to demonstrate reproducible IPS-induced PPR on EEG at ≥3 points. All five randomized participants completed the five-period crossover study. All participants were white and female (Table 1). The mean (SD) age was 27.2 (6.8) years and the mean (SD) BMI was 25.4 (3.5) kg/m².

3.2 | Photosensitivity range

All doses of Staccato alprazolam were effective in reducing the SPR at 2 minutes (the earliest measured time point; Figure 3). The effect was sustained through 4 hours for the 0.5-mg dose and 6 hours for the 1- and 2-mg doses. In a representative participant, Staccato alprazolam 1- and 2-mg doses suppressed photosensitivity through 6 hours compared with Staccato placebo; the effect of Staccato alprazolam 0.5 mg was sustained through 4 hours (Figure S1D). Results for all participants are shown in Figure S1.

3.3 | PD effect

A rapid and marked treatment effect was observed with Staccato alprazolam compared with Staccato placebo on measures of sedation (Figure 4) and sleepiness (Figure S2). The magnitude of effect was greater for the 2-mg dose and less for the 0.5-mg dose at all time points. The duration of sedation/sleepiness appeared to be dose-related.

3.4 | Pharmacokinetics

Mean alprazolam plasma concentrations were proportional to dose (Figure S3). The following alprazolam concentrations were observed by dose at the 2-minute time point: 0.5-mg dose, 5.14 ± 2.41 ng/mL; 1.0-mg dose, 12.7 ± 3.99 ng/mL; and 2.0-mg dose, 31.5 ± 3.14 ng/mL. The mean alprazolam Cmax (SD) coefficient of variation [CV%] was 5.62 ng/mL (1.84) [32.7], 13.60 ng/mL (3.00) [22.1], and 31.50 ng/mL (3.14) [9.9] for the 0.5-, 1.0-, and 2.0-mg Staccato alprazolam doses, respectively.

Mean Area under the concentration curve from 0 to the last measurable value (AUClast) (SD) [CV%] was 25.01 h*ng/mL (6.57) [26.3] for 0.5 mg Staccato alprazolam, 60.29 h*ng/mL (7.59) [12.6] for 1.0 mg Staccato alprazolam, and 113.0 h*ng/mL (16.61) [14.7] for 2.0 mg Staccato alprazolam.

3.5 | Safety

Four of five participants (80.0%) experienced at least 1 AE during the study. All AEs were mild or moderate in intensity. No participants experienced a severe or serious AE. There were no reports of dyspnea, wheezing, or other pulmonary AEs. The incidence of AEs tended to be greater in the

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TABLE 1 Participant demographics and baseline characteristics, N = 5

| Characteristic                  | Value |
|--------------------------------|-------|
| Age, y, median (range)         | 24 (23-39) |
| Female, n (%)                  | 5 (100) |
| BMI, kg/m², median (range)     | 25.2 (20.0-28.9) |
| Epilepsy type, n (%)           |       |
| Idiopathic generalized epilepsy| 5 (100) |
| Background AEDs, n (%)         |       |
| Levetiracetam                  | 3 (60) |
| Topiramate                     | 1 (20) |
| Zonisamide                     | 2 (40) |

Abbreviations: AED, antiepileptic drug; BMI, body mass index.

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FIGURE 2 Participant flow.
BMI, body mass index; EEG, electroencephalogram; IPS, intermittent photic stimulation; PPR, photoparoxysmal response
**FIGURE 3** Mean standardized photosensitivity range (SPR) over time

**FIGURE 4** Mean visual analog scale over time for sedation
Staccato alprazolam 2-mg treatment period (80.0%; Table 2). No participants discontinued the trial, and there were no clinically significant laboratory, vital sign, electrocardiographic, or physical examination findings identified over the course of the study.

4 | DISCUSSION

This is the first study of Staccato alprazolam and the first description of pulmonary-delivered antiseizure medicine administered to participants with a previous epilepsy diagnosis. Data from this proof-of-concept study showed that treatment with Staccato alprazolam was effective in reducing the SPR at the earliest measurable time point (2 minutes). Of note, given the time required to perform photic stimulation, an effect at times < 2 minutes could not be evaluated. A dose-related effect was apparent from 0.5 to 1 mg, but there was no apparent difference between the 1- and 2-mg doses on SPR; however, the sample size was too small to draw definitive conclusions. The effect was sustained through 4 hours for the 0.5-mg dose and 6 hours for the 1- and 2-mg doses. Importantly, the effect on SPR does not appear to be directly related to sedation caused by alprazolam, because the sedation associated with the 1- and 2-mg doses was either almost completely resolved or mostly resolved in the 4-6 hours postdose timeframe, whereas the effect on SPR for these higher doses in this same timeframe was still very apparent. Staccato alprazolam was generally well tolerated in this phase 2a study, and the AEs reported during this trial were similar to those reported for oral alprazolam or Staccato alprazolam for other indications.8,13

Given that this was a proof-of-concept study, it is unclear whether the ability to suppress photoepileptiform activity will translate into suppression of ongoing seizure activity. This ability will be explored in future efficacy trials. This proof-of-concept study did show that the Staccato system delivered a sufficient quantity of alprazolam to suppress photoepileptiform activity at an early time point. The rapidity of onset may suggest the ability to quickly suppress ongoing clusters of seizure activity, such as myoclonus, that may otherwise evolve into a generalized tonic-clonic convulsion. Moreover, in participants with a prolonged aura or focal seizure, a treatment that takes effect within no more than 2 minutes from administration may be able to shorten a seizure that is already underway. These opportunities and the feasibility of self-administration will need to be explored in further efficacy studies.

Maximum and total exposure to alprazolam after Staccato alprazolam dosing appeared to increase in a dose-proportional manner. The data show, as might be expected, a trade-off between efficacy (both quantity and duration) and tolerability. An ideal rescue therapy should act quickly to resolve seizures and allow a prompt return to normal activities after seizure cessation. In future trials of Staccato alprazolam, dosing should be explored with this in mind. Furthermore, the rapid onset of effect observed both in this trial and with PK data from a previous study suggests that Staccato alprazolam may enter the bloodstream more rapidly than what has been demonstrated for nonintravenously administered rescue benzodiazepines (5 minutes or more); further study is warranted to confirm this observation.

The main limitation of this proof-of-concept study is that the measurement of photosensitivity is time-consuming, and it was therefore not feasible to assess antiepileptic activity at <2 minutes after administration. Due to this limitation, it is possible that the onset of effect could have occurred earlier. Other limitations include the small sample size and strict inclusion criteria, which limit data generalizability to a broader population. Finally, antiseizure effect was measured indirectly in this study, and although these results are promising, further study to evaluate how well Staccato alprazolam suppresses seizure activity in participants with epilepsy is warranted.

### Table 2: AEs (incidence of ≥2 participants in any treatment group)

|                      | Staccato placebo, n = 5 | Staccato alprazolam 0.5 mg, n = 5 | Staccato alprazolam 1.0 mg, n = 5 | Staccato alprazolam 2.0 mg, n = 5 | Overall, n = 5 |
|----------------------|-------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------|
| Any AE               | 2 (40.0)                | 2 (40.0)                          | 3 (60.0)                          | 4 (80.0)                          | 4 (80.0)       |
| Cough                | 1 (20.0)                | 2 (40.0)                          | 1 (20.0)                          | 2 (40.0)                          | 2 (40.0)       |
| Diarrhea             | 2 (40.0)                | 0                                 | 0                                 | 0                                 | 2 (40.0)       |
| Dysgeusia            | 1 (20.0)                | 2 (40.0)                          | 2 (40.0)                          | 2 (40.0)                          | 2 (40.0)       |
| Oral dysesthesia     | 0                      | 2 (40.0)                          | 0                                 | 2 (40.0)                          | 2 (40.0)       |
| Sedation             | 0                      | 0                                 | 1 (20.0)                          | 2 (40.0)                          | 2 (40.0)       |
| Somnolence           | 1 (20.0)                | 1 (20.0)                          | 2 (40.0)                          | 2 (40.0)                          | 2 (40.0)       |

Note. Values are given as n (%).
Abbreviation: AE, adverse event.
In summary, this proof-of-concept study demonstrated that all three doses of Staccato alprazolam (0.5, 1.0, and 2.0 mg) rapidly suppressed epileptic activity in photosensitive participants with epilepsy. Sedation and somnolence were more prominent with higher doses. The AE profile of Staccato alprazolam was similar to what has been reported for alprazolam for other indications. The results support further development of Staccato alprazolam as a potential rescue medication for the acute treatment of seizures.

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CONFLICT OF INTEREST
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SUPPORTING INFORMATION

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

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