A Two-Part, Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of Staccato Alprazolam (STAP-001) in Patients with Epilepsy with a Predictable Seizure Pattern: Results from the Initial Open-Label Feasibility Part

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BACKGROUND

- The Staccato® system aerosolizes and delivers drug, via inhalation, deep into the lung for rapid systemic exposure
- A proof-of-concept study demonstrated that Staccato alprazolam (0.5, 1.0, and 2.0 mg) rapidly suppressed epileptiform activity at the 2-minute mark in photosensitive patients with an adverse event (AE) profile similar to what has been reported for alprazolam in other indications[1]
- In this two-part trial, we evaluated the efficacy and safety of Staccato alprazolam in patients with epilepsy with predictable seizure patterns

METHODS

- STAP-001 (NCT03478982) is a phase 2b study consisting of two parts, an open-label feasibility segment (Part 1) and a double-blind segment (Part 2); data from Part 1 are presented

Part 1: Open-label feasibility

- Eligible patients received a single dose of 1 mg STAP-001 at the onset of their predictable seizure episode and underwent evaluations
- Enrollment in Part 1 ended when data were obtained from ≥8 patients treated for a single seizure episode
- The feasibility data (emphasis on the drug administration and clinical assessment procedures) from patients in Part 1 were analyzed, reviewed, and adjudicated before starting Part 2, the double-blind part of the study

Patients

- Adult patients (≥18 years of age) with a diagnosis of focal and/or generalized epilepsy with a documented history of predictable seizure episodes, as listed below, were eligible to participate
  - Generalized seizure episodes starting with a flurry of absence seizures or myoclonic seizures with a minimum duration of 5 minutes
  - Episodes of a prolonged focal seizure with a minimum duration of 3 minutes
  - Episodes of multiple (≥2) seizures within a 2-hour time period
- Prior to randomization, patients must have experienced ≥4 seizure episodes with predictable pattern during the last 4 weeks (qualification period) and no more than one week without a predictable seizure episode before entry into the inpatient unit

Outcomes

- The primary efficacy outcome was the proportion of patients in each treatment group achieving seizure activity cessation within 2 minutes after the administration of the study drug and no recurrence of seizure activity within 2 hours (responders)
- Secondary efficacy endpoints included seizure episode severity (assessed by patient and/or caregiver), use of rescue medication, secondary generalization
- Safety was assessed by evaluating AEs, vital signs, clinical laboratory measures, and physical exams
- Blood samples were collected pre-dose, 10-, 30-, 60-, 120-, and 360-minutes post dose for pharmacokinetic evaluation

Statistical analysis

- Descriptive statistics were reported for Part 1
- Given the open-label design, no statistical comparisons were conducted

RESULTS

Patient demographics

Patient

- Eight patients were enrolled and completed Part 1 (**Table 1**)
- All patients were female with a mean age of 48.1 years and mean duration of epilepsy of 32.3 years
- Patients had the following predictable seizure episodes:
  - One patient with generalized seizures starting with a flurry of absence or myoclonic seizures (≥5-minute duration after recognition)
  - Four patients with episodes of a prolonged focal seizure (≥3-minute duration)
  - Three patients with ≥2 seizures within 2 hours

Table 1. Patient baseline demographics and characteristics

Parameter	N=8
Female, n (%)	8 (100.0)
Mean age (range), years	48.1 (24–69)
Mean duration of epilepsy (range), years	32.3 (7–63)
Seizure type, n (%)	
Focal	7 (87.5)
Generalized	1 (12.5)
Background AEDs,[a] n (%)	
Zonisamide	4 (50.0)
Levetiracetam	3 (37.5)
Lacosamide	2 (25.0)
Lamotrigine	2 (25.0)

[a] Incidence ≥2 patients.

Summary of patient data

- Two patients self administered Staccato alprazolam during their predictable seizure episode, and the remaining 6 patients had Staccato alprazolam administered by study staff or caregiver (**Table 2**)

Efficacy, Safety, and Pharmacokinetics Findings

Outcomes

- The responder rate in Part 1 was 62.5% (**Figure 1**)
- Responder rates by seizure subtypes, rescue medication usage, background AED inducer status, and BMI cutoff are shown in **Figure 1**
- No serious or severe adverse events were reported
- Review of other safety parameters (ie, general and neurological examinations, vital signs, laboratory values, and ECGs) did not reveal any safety concerns
- The plasma concentrations of alprazolam by patient over time are shown in **Figure 2**

Figure 2. Alprazolam plasma concentrations over time

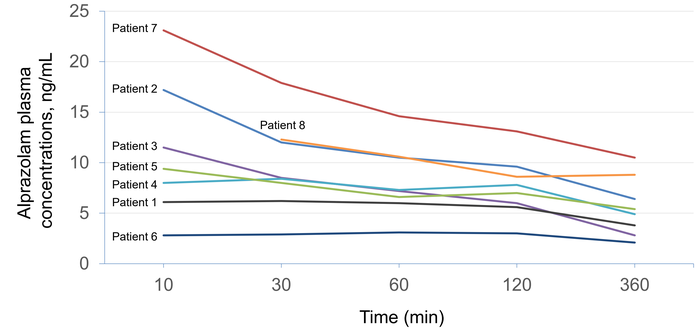

Figure 1. Responder rate by background status

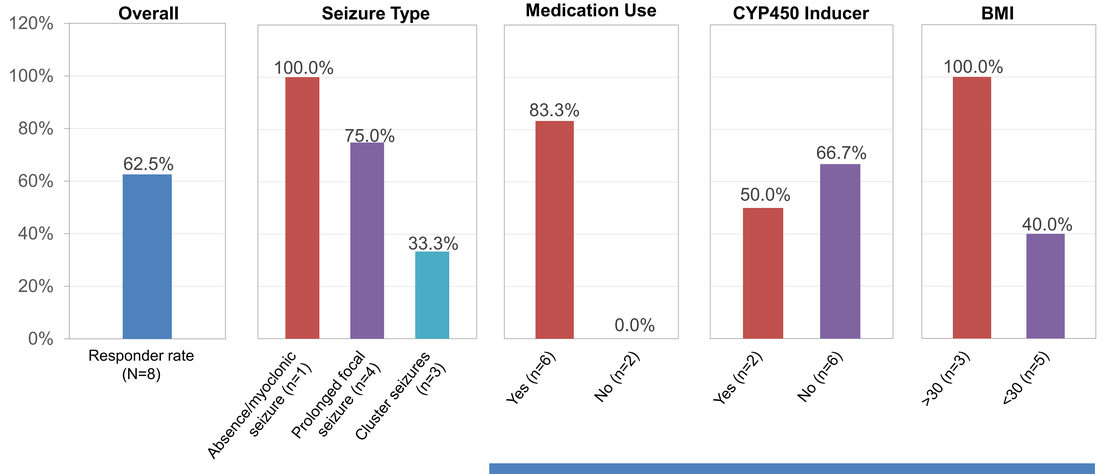

Table 2. Summary of patient responder status by seizure subtypes, rescue medication usage, background AED inducer status, and BMI

Patient	Responder	Seizure type	Secondary generalization	Use of rescue medication	Concomitant use of CYP450 Inducer	BMI (kg/m²)	Administration	C_{max} (ng/mL)
1	No	Cluster	No	No	No	21.8	Staff/Caregiver	6.2
2	Yes	PF	No	Yes	No	37.9	Self	17.2
3	No	Cluster	Yes	Yes	Yes	23.2	Staff/Caregiver	11.5
4	Yes	Cluster	No	Yes	Yes	27.8	Staff/Caregiver	8.4
5	Yes	PF	Yes	Yes	No	34.3	Staff/Caregiver	9.4
6	No	PF	Yes	No	No	25.7	Staff/Caregiver	3.1
7	Yes	Abs/MC	Yes	Yes	No	29.0	Staff/Caregiver	23.1
8	Yes	PF	Yes	Yes	No	35.4	Self	12.3

Abs, absence seizure; BMI, body-mass index; CYP450, cytochrome P450; MC, myoclonic seizure; PF, prolonged focal seizure.

CONCLUSIONS

- Part 1 of the study demonstrated successful enrollment in each predictable seizure eligibility category, and feasibility of study procedures for administration and dosing of 1 mg Staccato alprazolam
- No serious or severe adverse events were reported
- The treatment appeared efficacious with a 63% seizure response rate (5/8 responders) with the predefined responder criteria (seizure cessation in 2 minutes of Staccato alprazolam administration and no recurrence in 2 hours)
- The double-blind Part 2 of the study has been initiated and will randomize approximately 115 patients (n=105 successfully completing the study) to one of two active arms (Staccato alprazolam 1 mg or 2 mg) versus placebo

REFERENCE

1. French J, et al. *Neurology*. 2017;88(16 Supplement)P6.236.