A randomized Phase 2b efficacy study in patients with seizure episodes with a predictable pattern using Staccato® alprazolam for rapid seizure termination

Supporting Information

Full patient inclusion and exclusion criteria.

Inclusion criteria

1. Patient was able to provide written, personally signed, and dated informed consent to participate in the study or had a legally authorized representative sign the informed consent on his or her behalf before completing any study related procedures.
2. Male or female ≥18 years of age.
3. Has an established diagnosis of focal or generalized epilepsy or focal and generalized epilepsy with a documented history of predictable seizure episodes that includes at least one of the following:
    a. Generalized seizure episodes starting with a flurry of absence seizures or myoclonic seizures with a minimum duration of 5 mins
    b. Episodes of a prolonged focal seizure with a minimum duration of 3 mins
    c. Episodes of multiple (two or more) seizures within a 2-hour time period.
4. Before randomization, had experienced four or more seizure episodes with predictable pattern during the past 4 weeks (qualification period) and no more than 1 week without a predictable seizure episode before entry into the inpatient unit.
5. Female patients (if of childbearing potential and sexually active) and male patients (if sexually active with a partner of childbearing potential) who agreed to use a medically

acceptable and effective birth control method throughout the study and for 1 week following the end of the study. Medically acceptable methods of contraception that may have been used by the patients and/or his/her partner included: abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device, surgical sterilization, and progestin implant or injection. Prohibited methods included: the rhythm method, withdrawal, condoms alone, or diaphragm alone.

6. Patient was able to comply by the requirements of the protocol, particularly the requirements and specific institution policies during the inpatient stay.

Exclusion criteria*

1. History or diagnosis of nonepileptic seizures (eg, metabolic or pseudo-seizures).
2. History of status epilepticus in the 6 months before screening.
3. Had a progressive neurological disorder such as brain tumor, demyelinating disease, or degenerative central nervous system disease that was likely to progress in the next 3 months.
4. Use of strong cytochrome P450 (CYP) 3A4 inhibitors including; azole antifungal agents (eg, ketoconazole, itraconazole), nefazodone, fluvoxamine, cimetidine, human immunodeficiency virus (HIV) protease inhibitors (eg, ritonavir).
5. Had severe chronic cardio-respiratory disease.
6. History of HIV-positivity.
7. Pregnant or breastfeeding.
8. Clinically significant renal or hepatic insufficiency (hepatic transaminases more than two times the upper limit of normal (ULN) or creatinine ≥1.5 × ULN).

9. History of acute narrow angle glaucoma, Parkinson's disease, hydrocephalus, or history of significant head trauma.
10. Patients who used medications to treat airways disease, such as asthma or chronic obstructive pulmonary disorder, or had any acute respiratory signs/symptoms (eg, wheezing).
11. Used any investigational drug within 30 days or five half-lives of the investigational drug before administration of study drug, whichever was longer.
12. A history within the past 1 year of drug or alcohol dependence or abuse.
13. Positive urine screen for drugs of abuse at Screening (positive cannabis/cannabinol results were acceptable if there was a documented history of stable use for medical purposes).
14. Known allergy or hypersensitivity to alprazolam.
15. History of glaucoma.
16. Patients who had an active major psychiatric disorder for which changes in pharmacotherapy were needed or anticipated during the study.
17. Hypotension (systolic blood pressure ≤90 mmHg, diastolic blood pressure ≤50 mmHg), or hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥100 mmHg) measured while seated at screening or baseline.
18. Significant hepatic, renal, gastroenterologic, cardiovascular (including ischemic heart disease and congestive heart failure), endocrine, neurologic or hematologic disease.
19. Patients who, in the opinion of the investigator, should not participate in the study for any reason, including if there was a question about the stability or capability of the patient to comply with the study requirements.

*For the open-label feasibility part and any patients that were randomized before Protocol version 7, patients were excluded who were receiving chronic benzodiazepine treatment before admission to the inpatient unit.

Visual Analog Scale (VAS).

Sedation was assessed using a 100-mm linear VAS. Patients were given two scales, one anchored by “Sedated” and “Alert” on the left and right, respectively, and the other anchored by “Sleepy and “Awake” on the left and right, respectively. Patients placed a vertical mark on the line indicating their feelings in that moment of time, which was then measured in mm from the left, with lower scores indicating a higher level of sedation or sleepiness.

SUPPLEMENTAL TABLES

TABLE S1 Seizure episode severity (double-blind part; mITT/safety population)[a]

Seizure episode severity scale category, n (%)	**Staccato® placebo (n = 40)**	**Staccato® alprazolam**		
		1.0 mg (n = 38)	**2.0 mg (n = 38)**	**Combined active (n = 76)**
Much worse than	1 (2.5)	0	0	0
Worse than	2 (5.0)	1 (2.6)	2 (5.3)	3 (3.9)
Same as	17 (42.5)	22 (57.9)	21 (55.3)	43 (56.6)
Better than	14 (35.0)	7 (18.4)	11 (28.9)	18 (23.7)
Much better than	3 (7.5)	6 (15.8)	2 (5.3)	8 (10.5)
Not conducted	3 (7.5)	2 (5.3)	2 (5.3)	4 (5.3)

Abbreviation: mITT, modified intent-to-treat population.

[a]All 124 patients in the safety population were included in the mITT.

TABLE S2 Use of rescue medication (double-blind part; mITT/safety population)[a]

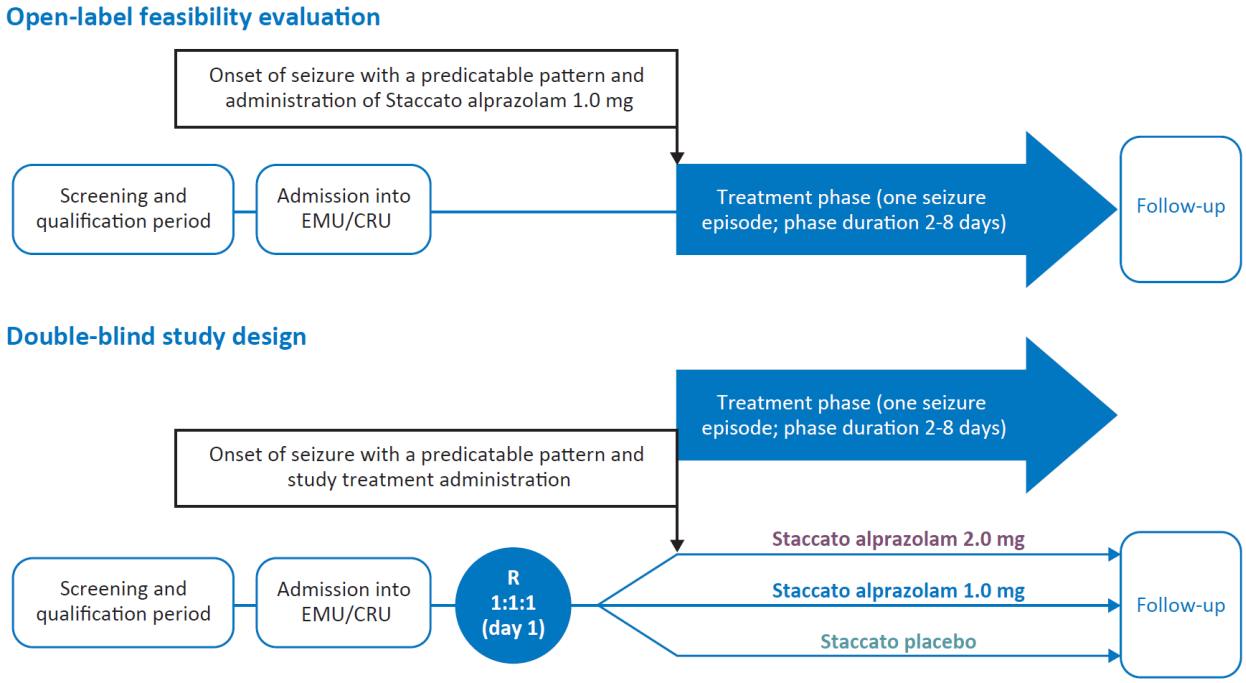
	Staccato®	**Staccato® alprazolam**		
	placebo (n = 40)	**1.0 mg (n = 38)**	**2.0 mg (n = 38)**	**Combined active (n = 76)**
Rescue medication used, n (%)	3 (7.5)	6 (15.8)	3 (7.9)	9 (11.8)

Abbreviation: mITT, modified intent-to-treat population.

[a]All 124 patients in the safety population were included in the mITT.

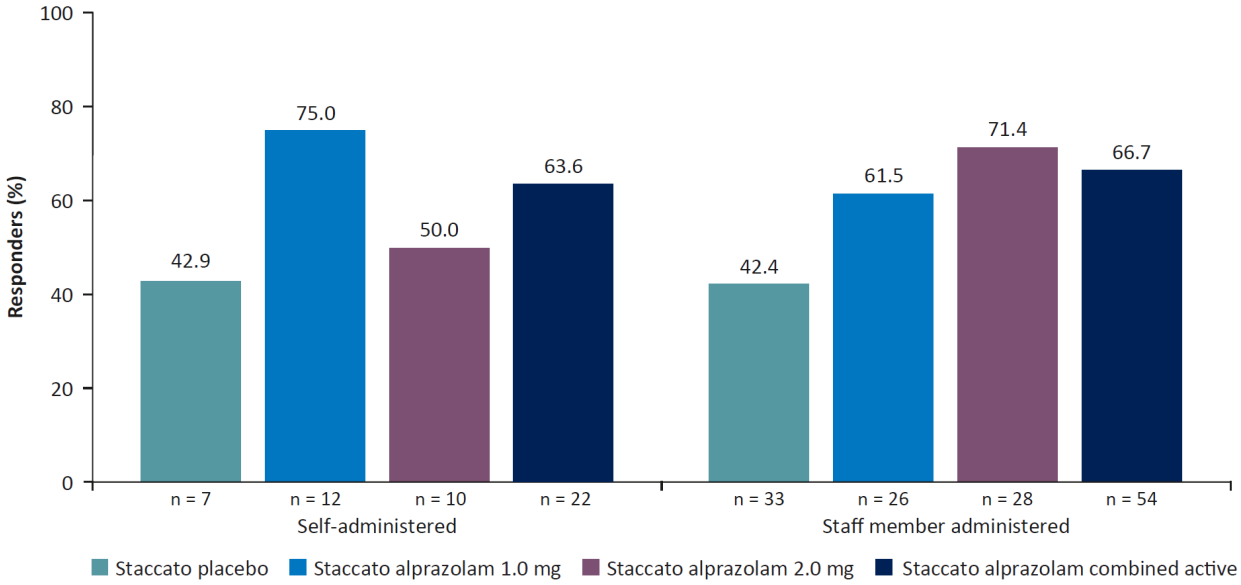
SUPPLEMENTAL FIGURES

FIGURE S1 Study design



Abbreviations: CRU, Clinical Research Unit; EMU, Epilepsy Monitoring Unit; R, randomization.

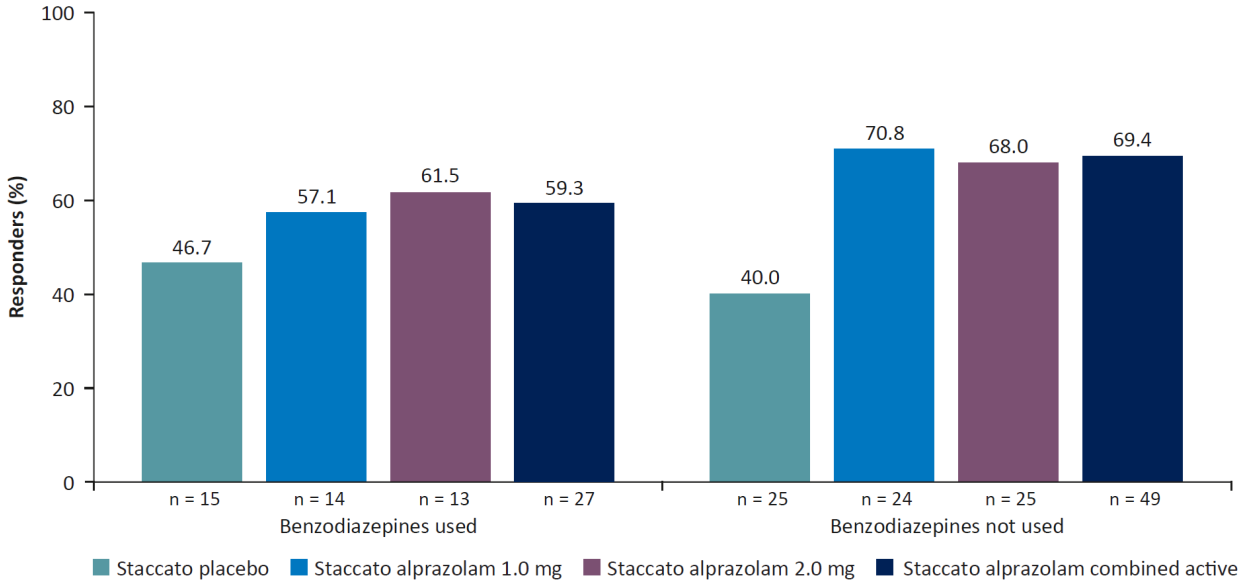
FIGURE S2 Proportion of responders[a] who (A) self-administered the study drug or (B) were administered the study drug by a staff member (double-blind part; mITT)



[a]Patients who achieved seizure activity cessation within 2 mins of treatment and no recurrence within 2 hours.

Abbreviation: mITT, modified intent-to-treat.

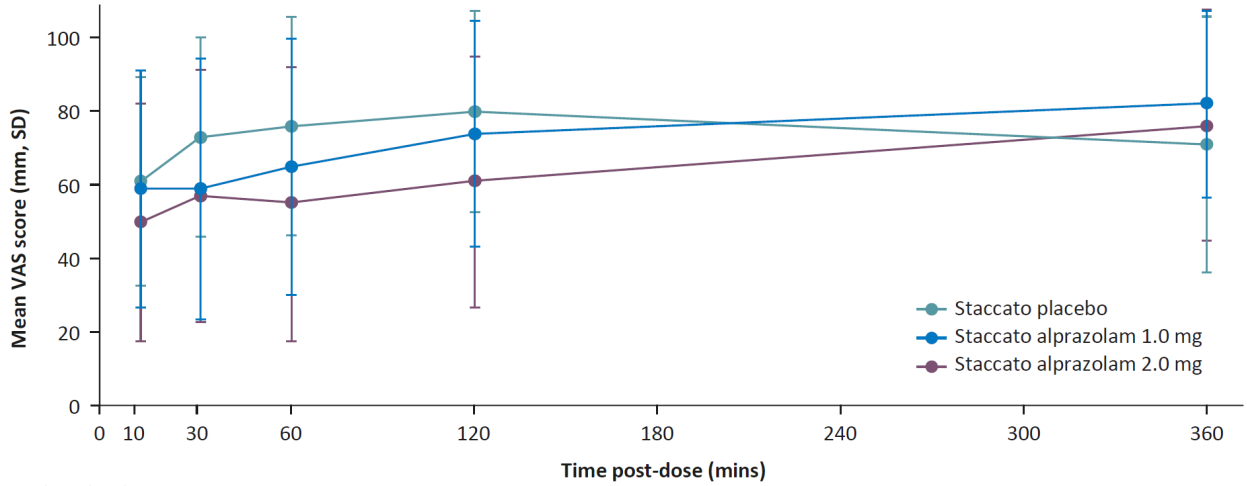
FIGURE S3 Proportion of responders[a] who (A) were taking chronic benzodiazepines or (B) were not taking chronic benzodiazepines (double-blind part; mITT)



Chronic benzodiazepine treatment was defined as an average of four or more administrations per week prior to admission to the inpatient unit. [a]Patients who achieved seizure activity cessation within 2 mins of treatment and no recurrence within 2 hours.

Abbreviation: mITT, modified intent-to-treat.

FIGURE S4 Sedation and alert VAS (double-blind part; safety population)



Number of patients						
Placebo	40	38	39	39	39	39
1.0 mg	38	36	36	36	36	37
2.0 mg	38	38	38	37	37	36

Lower VAS scores indicate a higher level of sedation.

Abbreviations: VAS, visual analog scale.

Appendix S1

Investigator appendix

The authors acknowledge the ENGAGE-E-001 study investigators for their contributions to data acquisition: Amza Ali, MD (Caribbean Institute of Medical Research [CARIMER], Kingston, Jamaica); Michael Amiri, MD (OnSite Clinical Solutions, LLC, Charlotte NC, USA); Anto Bagic, MD (University of Pittsburgh Medical Center, Pittsburgh, PA, USA); George Antony Barrio, MD (The NeuroMedical Institute, Panama City, FL, USA); Ramon Edmundo D. Bautista, MD (University of Florida Health Sciences Center Jacksonville, Jacksonville, FL, USA); Hai Chen, MD (GW Medical Faculty Associates, Washington, DC, USA); Steve Chung, MD (University of Arizona, Phoenix, AZ, USA); Kimberly S. Cruz, MD (Advanced Pharma, Miami, FL, USA); Jennifer DeWolfe, MD (University of Alabama Epilepsy Center, Birmingham, AL, USA); Dawn Eliashiv, MD (University of California Los Angeles, Los Angeles, CA, USA); Jessica Falco-Walter, MD (Stanford University, Palo Alto, CA, USA); Marc Frost, MD (DENT Neurologic Institute, Amherst, NY, USA); Eric Geller, MD (Institute of Neurology and Neurosurgery at Saint Barnabas, Livingston, NJ, USA); Arthur Grant, MD (The State University New York Downstate Medical Center, Comprehensive Epilepsy Center, Brooklyn, NY, USA); Hui Gong, MD (Rancho Research Institute, Downey, CA, USA); Lydie L. Hazan, MD (ACTCA, A Member of the Alliance, Inc., Los Angeles, CA, USA); Heidi Henninger, MD (Maine Medical Center, Scarborough, ME, USA); Robert Hogan, MD (Washington University School of Medicine, St. Louis, MO, USA); Omotola A. Hope, MD (University of Texas Health Science Center, Houston, TX, USA); Mercedes Jacobson, MD (Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA); Batool F. Kirmani, MD (Centra Medical Group Neurology Center, Lynchburg, VA, USA); Pavel Klein, MD (Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD, USA); Ruben Kuzniecky, MD

(Northwell Health, Lenox Hill, New York, NY, USA); Patrick Kwan, MD (Royal Melbourne Hospital, Parkville, VIC, Australia); Patrick Landazuri, MD (University of Kansas Medical Center, Comprehensive Epilepsy Center, Kansas City, KS, USA); Jong Woo Lee, MD (Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA); Ki Hyeong Lee, MD (AdventHealth Orlando [Florida Hospital], Orlando, FL, USA); Wei W. Ma, MD (JFK Medical Center, Edison, NJ, USA); Ram Mani, MD (Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA); Danielle McDermott, MD (University of Colorado, Denver, CO, USA); Ian O. Miller, MD (Nicklaus Children's Hospital, Miami, FL, USA); David Millett, MD (Hoag Hospital, Newport Beach, CA, USA); Saul Mullen, MD (Melbourne Brain Centre, Austin Health, Heidelberg, VIC, Australia); Rebecca O'Dwyer, MD (Rush University Medical Center, Chicago, IL, USA); Angela Peters, MD (University of Utah School of Medicine, Salt Lake City, UT, USA); Steven Phillips, MD (MultiCare Institute for Research and Innovation, Tacoma, WA, USA); James Ben Renfroe, MD (Northwest Florida Clinical Research Group, LLC, Gulf Breeze, FL, USA); Steven Hart Schechter, MD (Michigan Center of Medical Research, Farmington Hills, MI, USA); Stephan Schuele, MD (Northwestern University Feinburg School of Medicine, Chicago, IL, USA); Courtney Schusse, MD (St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA); Aashit Shah, MD (Carilion Clinic, Roanoke, VA, USA); Ajaz Sheikh, MD (University of Toledo Medical Center, Toledo, OH, USA); Rajdeep Singh, MD (Carolinas HealthCare System Neurosciences Institute, Charlotte, NC, USA); Adithya Sivaraju, MD (Yale University, New Haven, CT, USA); David Spencer, MD (Oregon Health & Science University [OHSU], Brain Institute, Comprehensive Epilepsy Center, Portland, OR, USA); Michael Sperling, MD (Thomas Jefferson University, Philadelphia, PA, USA); Daniel Tarquinio, MD (Center for Rare Neurological Diseases, Norcross, GA, USA); William Tatum, MD (Mayo

Clinic Florida, Jacksonville, FL, USA); Tricia Ting, MD (MedStar Georgetown University Hospital, Washington, DC, USA); Blanca Vazquez, MD (New York University Langone Comprehensive Epilepsy Center, New York, NY, USA); Thomas Wychowski, MD (University of Rochester Medical Center, Rochester, NY, USA); Ji Yeoun Yoo, MD (Mount Sinai Health System, New York, NY, USA).