DIAZEPAM BUCCAL FILM (DBF): FINAL RESULTS FROM A PHASE 3, OPEN-LABEL, SAFETY AND TOLERABILITY STUDY OF CHRONIC INTERMITTENT USE IN PEDIATRIC, ADOLESCENT AND ADULT SUBJECTS WITH EPILEPSY

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INTRODUCTION

- Available treatments for seizure clusters in patients with epilepsy are suboptimal, particularly in terms of speed of onset of action and ease of administration[2,4,5]
- Currently, diazepam rectal gel, Diazepam Nasal Spray, and midazolam nasal spray are the only treatments approved by the United States Food and Drug Administration for refractory patients with epilepsy experiencing bouts of increased seizure activity[6,7] but both can be associated with difficulties in adherence and unpredictable pharmacokinetics[1,5,8,9]
- Diazepam buccal film (DBF) is a novel formulation of diazepam in development that is designed to be easily administered,[10] with a more consistent, predictable pharmacokinetic profile compared with rectally administered diazepam[11]
- The diazepam pharmacokinetics following DBF administration have been evaluated in six Phase 1 clinical studies in healthy volunteers, two Phase 2 clinical studies in adults with epilepsy, and one Phase 2 clinical study in pediatric subjects with epilepsy.
- This Phase 3 study was undertaken to evaluate the safety and tolerability of DBF used over the long-term in the intended population. It was designed to determine if DBF could be successfully and safely self-administered or with the help of a caregiver in the outpatient setting and help patients experiencing seizure clusters achieve seizure cessation, reduce seizure-related complications, and prevent progression to more serious sequelae.

OBJECTIVES

- *Primary objective*:
  - To assess the safety and tolerability of DBF (study drug) administered a minimum of 3 times to subjects with epilepsy for the treatment of seizures over a minimum 6-month period.
- *Secondary objectives:*
  - To evaluate the usability of study drug as assessed by the ability of caregivers/subjects to administer study drug based on the Instructions for Use (IFU).
  - To evaluate the Quality of Life (QoL) of the subjects during the study drug treatment period as assessed by use of age-appropriate epilepsy scales over a minimum 6-month period.

METHODS

STUDY DESIGN

- This was a Phase 3, multicenter, open-label, long-term safety and tolerability study of chronic, intermittent use of DBF.
- An overview of the study schema is shown in **Figure 1.**

Figure 1. Study Schema

PATIENTS

- The study population was male and female children (2 to 12 years old), adolescents (13 to 16 years old), and adults (17 to 65 years old) with a clinical diagnosis of epilepsy and with bouts of increased seizure activity, frequent breakthrough seizures, seizure clusters, or cluster seizures and who were on chronic, intermittent use of a rescue medication.

PROCEDURES AND ASSESSMENTS

- Informed consent was obtained prior to study entry
- Patients and caregivers were trained on how to administer DBF and use of an electronic diary to document administration and usability, as well as to capture seizure history and changes in health and medications.
- DBF was administered for breakthrough seizures; a second dose could be used in 4 to 12 hours after first if necessary but no more than 1 episode every 5 days.
- DBF was dispensed at weight- and age-based doses ranging from 5 to 17.5 mg, which could be adjusted with aging or change in body weight during the study. Modest adjustments to dose could also be made clinically depending on initial response

OUTCOMES OF INTEREST FOR THE CURRENT ANALYSIS

- Primary outcomes included: treatment-emergent adverse events (TEAEs), including relationship to treatment with study drug and severity, suicidal ideation and activity in appropriately aged subjects using the Columbia Suicide Severity Rating Scale (C-SSRS), vital signs and laboratory analyses and pathological change in oral mucosa and gustatory sense changes
- Secondary outcomes included: Quality of Life by use of age-appropriate epilepsy scales, DBF administration and usability, as assessed by patients and/or caregivers, recorded after each use of study drug, including successful placement/buccal insertion of DBF, oral cavity retention of DBF, and ability to open packaging and remove DBF

DATA ANALYSIS

- Analyses for this study were descriptive only. No inferential statistical analyses were planned. Statistical methodology and analyses are in accordance with the principles outlined by the International Conference on Harmonization (ICH) E9 guidelines.
- All statistical analyses were done using SAS statistical software version 9.3 or higher.

RESULTS

STUDY PATIENTS

- A total of 167 subjects with epilepsy (25 children ages 2 to 11 years, 26 adolescent ages 12 to 16 years, and 116 subjects age 17 years and older) were screened for enrollment eligibility in this study;
- 150 participants who passed screening were enrolled and of the 150 subjects enrolled in the study, 130 (86.7%) received at least 1 dose of DBF for a breakthrough seizure and were included in the Safety Analysis Set and 108 subjects (72%) completed the study.
- Patient demographics and baseline characteristics are shown in **Table 1.**

TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Age 2 - 5 (N=3)	Age 6 - 11 (N=15)	Age 12 - 16 (N=20)	Age ≥ 17 (N=92)	Overall (N=130)
Age, mean (SD), years	4.3 (0.58)	9.1 (1.88)	14.3 (1.45)	31.8 (11.06)	25.9 (13.28)
Female, n (%)	2 (66.7)	8 (53.3)	12 (60.0)	44 (47.8)	66 (50.8)
Race, n (%)					
White	2 (66.7)	12 (80.0)	15 (75.0)	70 (76.1)	99 (76.2)
Black or African American	0	2 (13.3)	3 (15.0)	7 (7.6)	12 (9.2)
Asian	0	0	1 (5.0)	4 (4.3)	5 (3.8)
Native Hawaiian or Other Pacific Islander	0	0	0	6 (6.5)	6 (4.6)
Other[a]	1 (33.3)	1 (6.7)	1 (5.0)	5 (5.4)	8 (6.2)
Ethnicity, n (%)					
Hispanic or Latino	2 (66.7)	3 (20.0)	4 (20.0)	20 (21.7)	29 (22.3)
Not Hispanic or Latino	1 (33.3)	12 (80.0)	16 (80.0)	70 (76.1)	99 (76.2)
Unknown	0	0	0	2 (2.2)	2 (1.5)
BMI (kg/m^2), mean (SD)	16.9 (4.51)	17.5 (2.53)	20.4 (3.29)	26.2 (6.76)	24.1 (6.81)
Duration of epilepsy (years), mean (SD)	4.0 (0.00)	7.9 (2.37)	7.7 (5.07)	19.2 (10.89)	15.8 (10.82)

BMI, body mass index; SD, standard deviation.

DBF SAFETY

- An overview of TAEs is shown in **Table 2**
  - 382 TEAEs were reported for 84/130 (64.6%) subjects who received at least 1 dose of DBF for treatment of seizures, from which 27 were clinically significant (severe intensity) and occurred in 14/130 (10.8%) subjects. Of note, only 12 of the total 382 TEAEs were considered related to DBF by the Investigator.
  - The most frequently reported TEAE was seizure (98 events reported for 26 subjects).
  - A total of 23 serious adverse events (SAEs) were reported in 18 subjects (13.8%) over the course of the study, occurring most commonly in the ≥ 17 years age group with 15 SAEs reported in 10 subjects (10.9%). The most commonly reported SAEs were seizures (5 events reported for 5 subjects).
  - Three SAEs had an outcome of death. One death was attributed to sudden unexplained death in epilepsy (SUDEP), 1 death was attributed to epileptiform seizure, and the third death was attributed to brain malignancy. All were determined to be unrelated to DBF.

TABLE 2. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS

Parameter	Overall (N=130)
	Number (%) of Patients, [Number of Events]
Any TEAE	84 (64.6) [382]
Any Serious TEAE	18 (13.8) [23]
Any Related TEAE	10 (7.7) [12]
Any Severe TEAE	14 (10.8) [27]
Any Severe and Related TEAE	1 (0.8) [1]
Any AE leading to Death	3 (2.3) [3]
Any Related AE leading to Death	0

TABLE 3. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST OVERALL – SAFETY ANALYSIS SET

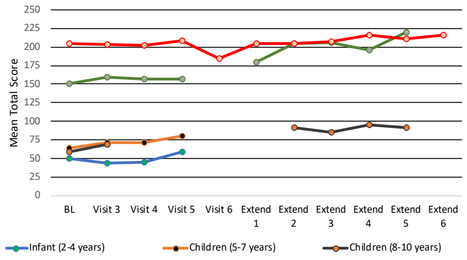
Parameter	Overall (N=130) Number (%) of Patients, [Number of Events]
ORAL IRRITATION ADVERSE EVENTS	
Subjects with Any Adverse Events of Special Interest	3 (2.3) [3]
Mouth swelling	1 (0.8) [1]
Gingivitis	1 (0.8) [1]
Lip injury	1 (0.8) [1]
ORAL SAFETY ADVERSE EVENTS	
Subjects with Any Adverse Events of Special Interest	8 (6.2) [11]
Toothache	2 (1.5) [2]
Gingival pain	1 (0.8) [1]
Mouth haemorrhage	1 (0.8) [1]
Mouth ulceration	1 (0.8) [1]
Oral discomfort	1 (0.8) [1]
Stomatitis	1 (0.8) [1]
POTENTIAL ABUSE RELATED ADVERSE EVENTS	
Subjects with Any Adverse Events of Special Interest	21 (16.2) [28]
Somnolence	6 (4.6) [6]
Lethargy	4 (3.1) [5]
Stress	3 (2.3) [3]
Confusional state	1 (0.8) [1]
Emotional distress	1 (0.8) [1]
Irritability	1 (0.8) [1]
Mood swings	1 (0.8) [1]

- Three oral irritation AEs (mouth swelling, gingivitis, and lip injury) were reported for 3 subjects (2.3%) overall.
- Eleven oral safety AEs were reported for 8 subjects (6.2%). The most common TEAE in this category was toothache (2 events reported for 2 subjects). All other oral safety AEs were solitary events reported in no more than 1 subject.
- Twenty-eight potential abuse-related AEs were reported for 21 subjects (16.2%) overall. Somnolence was the most commonly reported TEAE in this category: 6 events in 6 subjects (4.6%) followed by lethargy, 5 events in 4 subjects (3.1%). Other TEAEs in this category that were reported as multiple events in more than 1 subject were stress (3 events in 3 subjects [2.3%]); 2 events of ataxia, vertigo, and gait disturbance were reported in 2 subjects each (1.5%).

TOLERABILITY – QUALITY OF LIFE ASSESSMENTS

- **Figure 2** plots mean scores obtained at each visit and shows an upward trend in mean scores in all age groups over the course of the study.

Figure 2. Summary of Quality-of-Life Scores (Safety Analysis Set)



BL = Baseline visit; Visit 6 serves as the Final/Completion site visit. The Sponsor elected to extend the study beyond Visit 6 under a similar schedule of visits for some subjects (with the agreement/recommendation of the Investigator and the subject and/or caregiver as applicable). Extend 1-6 after Visit 6 indicate extended visits.

- Metrics studied for the quality-of-life evaluations were impact, cognitive functioning, sleep/fatigue, executive functioning, mood/behavior, general health, effects of epilepsy and AEDs, and overall quality of life.

DBF USABILITY

- A total of 1348 DBF use occasions were recorded in the electronic diary for 109 subjects overall. Of these 1348 use occasions, 1336 resulted in exposure to a dose of study drug.
- The average number of DBF attempted use occasions per subject was 12.7 (range 1 to 77).
- All 109 subjects had at least 1 successful buccal insertion occasion. All but 1 subject (<1%) had at least 1 successful placement of DBF on the first attempt in 1 of their dosing occurrences.
- 1268 (94%) of the film insertions were successfully placed against the buccal mucosa on the first attempt by the study subject or with the help of a parent/caregiver. In the majority of occasions, the film was placed successfully on a subsequent insertion attempt.
- There were no administration-related injuries during buccal placement, including biting injuries, to either caregiver or patient
- A total of 29 subjects (ages 14 to 62) self-administered at least 1 DBF dose over the course of the study. The total number of self-administered doses overall for the 29 subjects was 214 (mean 7.4; range 1 to 28 doses).
- DBF doses were administered throughout the seizure event life cycle (ie, periictal, ictal, and post-ictal). A total of 619 (47.7%) of the total use occasions occurred from the time of seizure to 5 minutes after the seizure **(Table 4).**

TABLE 4. SUMMARY OF FIRST DBF DOSE OCCASION TIMING IN RELATION TO SEIZURE ACTIVITY

Statistics	Overall: E (%) (167)/ N = 1297
1 hour to 5 minutes BEFORE seizure	72 (5.6%) (33)
5 minutes BEFORE seizure to start of seizure	72 (5.6%) (29)
at time of seizure to 5 minutes AFTER seizure	619 (47.7%) (85)
AFTER seizure > 5 minutes to 30 minutes	357 (27.5%) (70)
> 30 minutes AFTER seizure	177 (13.6%) (62)

Abbreviations: E (%) = number and percentage of occasions, (n)= number of subjects, N= total use occasions.

CONCLUSIONS

- In this observational study of chronic, intermittent administration and use, DBF was found to be safe and well tolerated by pediatric, adolescent, and adult patients with epilepsy experiencing seizure emergencies
- In all age groups and all onset doses, the majority of TEAEs were mild to moderate and transient in nature.
- Treatment-related AEs were infrequent with the vast majority being of mild severity
- Quality of life assessments indicated an upward trend (improvement) in mean scores in all age groups over the duration of the study.
- Administration was successful on 99% of use occasions
- 94% (1268) of the film insertions were successfully placed against the buccal mucosa on the first attempt
- There were no administration-related injuries during buccal placement, including biting injuries, to either caregiver or patient
- Tracking DBF usability over the course of the study demonstrated the potential for self-administration and DBF can be successfully dosed throughout the seizure event life cycle.
- These observations show DBF is a safe, generally well-tolerated, and usable treatment for chronic intermittent use as a rescue medication for patients with epilepsy.

REFERENCES

1. Jafarpour S, *et al. Seizure.* 2019;68:9-15. **2.** Penovich PE, *et al. Neurologist.* 2017;22:207-14. **3.** Sillanpaa M, Schmidt D. *Brain.* 2008;131:938-44. **4.** Tatum IW. *Epilepsy Behav.* 2002;3:535-8. **5.** Cereghino JJ. *Curr Treat Options Neurol.* 2007;9:249-55. **6.** Diastat C-IV (diazepam rectal gel) [package insert]. San Antonio, TX: DPT Laboratories; 2016. **7.** Nayzilam [package insert]. Smyrna, GA: UCB, Inc.; 2019. **8.** Fisgin T, *et al. J Child Neurol.* 2002;17:123-6. **9.** Haut SR, *et al. Epilepsy Behav.* 2016;63:109-17. **10.** Jung C, *et al.* Presented at: Annual Meeting of the American Epilepsy Society; November 30-December 4, 2018; New Orleans, LA. **11.** Heller AH, *et al. Neurology.* 2018;90(15 suppl):P4.273.

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