Safety of Diazepam Buccal Film in Children with Epilepsy: Subgroup Results from a Phase 3, Open-Label, Safety and Tolerability study

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INTRODUCTION

- Epilepsy is one of the most common neurologic disorders seen in children, affecting one to two percent of children worldwide. It is estimated up to 14% of children continue to have seizures despite being treated with antiseizure medications.
- Use of rescue medications in acute management of seizure clusters can help avoid progression to status epilepticus and reduce emergency room visits, yet 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 boutsof 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]
- This Phase 3 study was undertaken to evaluate the safety and tolerability of DBF used over the long-term in children, adolescent and adult populations. We analyze a subset of pediatric data to determine if DBF could achieve seizure cessation, reduce seizure-related complications, and prevent progression to more serious sequelae among younger patients.

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 in a pediatric population (<17 years old).
- *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 **Figure1.**

Figure 1. Study Schema

PATIENTS

- For the subset analysis, the study population was male and female children (2 to 12 years old), and adolescents (13 to 16 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, vital signs and laboratory analyses, and pathological change in oral mucosa and gustatory sense changes for those aged 12 and older.
- 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

- Analysis of pediatric data was performed. Analyses 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 51 pediatric subjects with epilepsy (25 children ages 2 to 11 years, 26 adolescent ages 12 to 16 years) were screened for enrollment eligibility in this study; among them, 38 subjects (3 children ages 2-5, 15 ages 6-11 and 20 ages 12-16 years old) completed the study and were included in the Safety Analysis Set.
- Within the 2 to 5 years and the 12 to 16 years cohort, most subjects (60% to 66.7%) were female. Developmental delay and/or cognitive disorders were reported for all subjects in the 2 to 5 years and 6 to 11 years age cohorts and were reported for all except 3 subjects in the 12 to 16 years age cohort.
- 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, mean (SD), years	4.3 (0.58)	9.1 (1.88)	14.3 (1.45)
Female, n (%)	2 (66.7)	8 (53.3)	12 (60.0)
Race, n (%)			
White	2 (66.7)	12 (80.0)	15 (75.0)
Black or African American	0	2 (13.3)	3 (15.0)
Asian	0	0	1 (5.0)
Native Hawaiian or Other Pacific Islander	0	0	0
Other[a]	1 (33.3)	1 (6.7)	1 (5.0)
Ethnicity, n (%)			
Hispanic or Latino	2 (66.7)	3 (20.0)	4 (20.0)
Not Hispanic or Latino	1 (33.3)	12 (80.0)	16 (80.0)
Unknown	0	0	0
BMI (kg/m^2), mean (SD)	16.9 (4.51)	17.5 (2.53)	20.4 (3.29)
Duration of epilepsy (years), mean (SD)	4.0 (0.00)	7.9 (2.37)	7.7 (5.07)

BMI=body mass index; SD=standard deviation

DBF SAFETY

- An overview of TAEs is shown in **Table 2**
  - 110 TEAEs were reported for 28/38 (73.7%) subjects who received at least 1 dose of DBF for treatment of seizures, from which only 4 were clinically significant (severe intensity) and occurred in 4/38 (10.5%) subjects.
  - In all age groups and all onset doses, the majority of TEAEs were mild to moderate and transient in nature. Of note, only 3 TEAEs were considered related to DBF by the investigator among pediatric subjects, none in the youngest age group to a maximum of 2 of 51 TEAEs in the 12 to 16 years age group.
  - No severe, serious, AESI, or AEs leading to discontinuation were reported for the 3 subjects in the 2-5 years age group. Only 6 AESI were reported in the 12 to16 years and 7 in the 6 to 11 years age groups, respectively.
  - Only 1 TEAE led to study drug discontinuation among pediatric subjects – pregnancy in 1 subject in the 12 to 16 years age group, which was not related to DBF.
  - The most commonly reported TEAE in the 12 to 16 was seizure with13 events reported for 10 (50%) subjects aged 12 to 16 years.
  - In subjects in the 6 to 11 years age group, TEAEs considered Infections and Infestations were the most common: 17 events reported for 7 subjects (46.7%). Sinusitis (3 cases in 3 subjects) was the most common TEAE.

TABLE 2. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS BY AGE GROUPS

Parameter	Age 2 - 5 (N=3)	Age 6 - 11 (N=15)	Age 12 - 16 (N=20)
Number (%) of Patients, [Number of Events]			
Any TEAE	1 (33.3) [6]	10 (66.7) [53]	17 (85.0) [51]
Any Serious TEAE	0	3 (20.0) [3]	5 (25.0) [5]
Any Related TEAE	0	1 (6.7) [1]	2 (10.0) [2]
Any Severe TEAE	0	3 (20.0) [3]	1 (5.0) [1]
Any Severe and Related TEAE	0	1 (6.7) [1]	0
Any AESI	0	5 (33.3) [7]	5 (25.0) [6]
Any AE leading to Study Drug Discontinuation	0	0	1 (5.0) [1]
Any AE leading to Death	0	0	1 (5.0) [1]
Any Related AE leading to Death	0	0	0

AE = adverse event; AESI = adverse event of special interest; TEAE = treatment-emergent adverse event.

- An overview of Treatment-emergent AESI by age groups is shown in **Table3.**
  - No oral irritation or oral safety related TEAEs were reported in either the 2 to 5 years age group or the 6 to 11 years age group.
  - Only 3 oral safety related AEs were reported in the 12 to 16 years age group. TEAEs of this nature were most commonly gastrointestinal Disorders.
  - 4 TEAEs identified as potential abuse related events were reported for 3 subjects (6 to 11 years age group) and 2 events in 2 subjects (12 to 16 years age group).
  - Other AESIs were TEAEs related to aspiration and respiratory failure and were reported in the 6 to 11 years age group. The most common TEAE in this category was dizziness, but none among pediatric subjects.

TOLERABILITY – QUALITY OF LIFE ASSESSMENTS

- 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.
- Mean scores obtained at each visit and shows an upward trend in mean scores in all 3 age groups for the pediatric populations over the course of the study.

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

Parameter	Age 2 - 5 (N=3)	Age 6 - 11 (N=15)	Age 12 - 16 (N=20)
Number (%) of Patients, [Number of Events]			
ORAL IRRITATION ADVERSE EVENTS			
Subjects with Any Adverse Events of Special Interest	0	0	1 (5.0) [1]
Mouth swelling	0	0	1 (5.0) [1]
Gingivitis	0	0	0
Lip injury	0	0	0
ORAL SAFETY ADVERSE EVENTS			
Subjects with Any Adverse Events of Special Interest	0	0	2 (10.0) [3]
Toothache	0	0	0
Gingival pain	0	0	0
Mouth haemorrhage	0	0	0
Mouth ulceration	0	0	1 (5.0) [1]
Oral discomfort	0	0	0
Stomatitis	0	0	1 (5.0) [1]
Tongue injury	0	0	0
POTENTIAL ABUSE RELATED ADVERSE EVENTS			
Subjects with Any Adverse Events of Special Interest		3 (20.0) [4]	2 (10.0) [2]
Somnolence	0	1 (6.7) [1]	1 (5.0) [1]
Lethargy	0	1 (6.7) [1]	0
Atxia	0	1 (6.7) [1]	0
Balance disorder	0	0	0
Stress	0	0	0
Confusional state	0	0	0
Emotional distress	0	0	0
Irritability	0	0	0
Mood swings	0	0	1 (5.0) [1]

DBF USABILITY

- **Table 4** summarizes the number of DBF use occasions (successful, close calls, and use errors) derived from e-diary entries over the course of the study.
- A total of 283 DBF use occasions were recorded in the electronic diary for 29 pediatric subjects overall. Of these 283 use occasions, 279 resulted in exposure to a dose of study drug (98.6%).
- All pediatric 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.
- 269 (95%) 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.
- All film insertion among subjects ages 2-5 were successful on the first attempt and no there were no injury to the patient or caregiver related to the insertion of the film.
- Only 14 (4.9%) close calls (defined as an instance/use occasion in which a user ultimately successfully completed the task; however, they experienced confusion, misinterpretation of instructions, or difficulty) were reported in this study. Most close calls were due to jaw clenching, drooling, and spitting out of the film before adhesion.

TABLE 4. SUMMARY OF SAFETY ANALYSIS SET (e-DIARY DATA) BY AGE GROUPS

Parameter	Age 2 - 5 (N=3)	Age 6 - 11 (N=15)	Age 12 - 16 (N=20)
Number of Use Occasions E (%) [N]			
Number of total use / attempted use occasions	24 / 1	94 / 11	165 / 17
Number of occasions with successful insertion/retention in cheek	24 (100%) [1]	94 (100%) [11]	161 (97.6%) [17]
Number of occasions where it took 1 attempt to insert film	24 (100%)[1]	89 (94.7%)[11]	156 (94.5%)[16]
Number of occasions where it took more than 1 attempt to insert film	0	5 (5.3%) [4]	5 (3.1%)[4]
Reasons for multiple insertion attempts/close calls			
Clenching jaw / won't open mouth	0	2 (2.1%)	1 (0.6%)
Excessive drooling	0	2 (2.1%)	2 (1.2%)
Other (none of the above)	0	2 (2.1%)	4 (2.4%)
Spit out before sticking	0	1 (1.1%)	0 (0.0%)0
Number of occasions where study drug was not successfully placed/retained in cheek	0	0	4 (2.0%)

CONCLUSIONS

- This study show DBF is a safe, generally well-tolerated, and usable treatment for chronic intermittent use as a rescue medication for pediatric patients with epilepsy.
- In all age groups, the majority of TEAEs were mild to moderate and transient in nature. No severe, serious, AESI, or AEs leading to discontinuation were reported for the 3 subjects in the 2-5 years age group.
- Only 3 TEAEs were considered related to DBF by the investigator among pediatric subjects, none in the youngest age group and 2 in the 12 to 16 years age group.
- Quality of life was evaluated using age-appropriate epilepsy scales over the duration of the study. Mean scores obtained at each visit indicated an upward trend in mean scores in all pediatric age groups over the course of the study.
- 98.6% of DBF use occasions that were recorded in the electronic diary for 29 pediatric subjects overall resulted in ingestion of a dose of study drug.
- All pediatric subjects had at least 1 successful buccal insertion occasion.
- 95% (269) 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.
- No injury to the patient or caregiver related to the insertion of the film were reported in the study.

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