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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

# Safety and tolerability associated with chronic intermittent use of diazepam buccal film in adult, adolescent, and pediatric patients with epilepsy

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## Abstract

**Objective:** Diazepam buccal film (DBF) is in development for treatment of patients experiencing bouts of increased seizure activity. We assessed safety, tolerability, and usability of self- or caregiver-administered DBF in the outpatient setting.

**Methods:** Patients aged 2-65 years needing treatment with a rescue benzodiazepine at least once monthly were eligible for the study. DBF (5-17.5 mg) was dispensed based on age and body weight. Patients/caregivers administered DBF for up to five seizure episodes per month. Adverse events (AEs) and usability assessments were recorded after the first dose, then every 3 months.

**Results:** Onehundred eighteen patients who used ≥1 DBF dose (adults, n = 82; adolescents, n = 19; children, n = 17) were enrolled. Eleven treatment-related AEs (10 being mild or moderate in severity) occurred in nine (7.6%) patients over a mean of 243 days of follow-up. No patient discontinued participation because of AEs. Mild local buccal discomfort, buccal swelling, and cheek skin sensitivity were reported by one patient each. Twenty-two serious AEs were reported; one was treatment-related. The three deaths reported, all unrelated to DBF, resulted from seizures or seizure with brain malignancy. Self-administration by adults was attempted on 23.6% (188/795) of use occasions. Administration of DBF occurred under ictal or peri-ictal conditions on 49.5% (538/1087) of use occasions, and DBF was successfully administered on a first or second attempt on 96.6% (1050/1087) of use occasions. Overall, patients received their dose of DBF on 99.2% (1078/1087) of use occasions. A second DBF dose was required within 24 hours after the first dose on 8.5% (92/1087) of use occasions.

**Significance:** In this observational study of chronic intermittent use, DBF was easy to administer, safe, and well tolerated in adult, adolescent, and pediatric patients with epilepsy experiencing seizure emergencies. DBF can be readily self-administered by adults with epilepsy, as well as successfully administered by a caregiver in seizure emergencies.

KEYWORDS
benzodiazepines, rescue, safety, seizures

## 1 | INTRODUCTION

Epilepsy affects an estimated 70 million people worldwide and 3.4 million people in the USA, including 3 million adults and 470 000 children.[1,2] Despite treatment with antiepileptic medications, many people with epilepsy experience cluster seizures and other bouts of more frequent or more severe seizures that increase their risk of injury, hospitalization, status epilepticus, and death.[3-5]

Seizure emergencies are usually treated with benzodiazepines[3,4,6,7]; however, currently available benzodiazepine formulations are suboptimal in terms of onset of action, dosing accuracy, portability, ease of administration, and route of administration.[4,8,9] Orally administered lorazepam or diazepam tablets are often used off-label for outpatient treatment of seizure emergencies, but these formulations have a relatively slow rate of absorption and are associated with increased risks of choking and aspiration.[9-11] There are no oral or buccal formulations currently approved for managing cluster seizures in the USA. The only treatments currently approved by the US Food and Drug Administration to control bouts of increased seizure activity are diazepam rectal gel (DRG) and intranasal formulations of midazolam and diazepam.[3,6,9,12,13] Although rectal and intranasal formulations may be absorbed more rapidly than oral tablets, they have several limitations. Rectal administration may be difficult, time-consuming, and embarrassing or socially awkward for patients and/or caregivers.[3,14-16] Intranasal administration can increase mucosal secretions, which can result in unpredictable absorption,[9] and intranasal formulations are not approved for patients ≤6 years of age.[13] Additionally, the complexities of carrying intranasal formulations and administering them during a seizure emergency may present difficulties for caregivers.

Diazepam buccal film (DBF) is a novel formulation of diazepam that is in development as an alternative approach to control episodes of increased seizure activity in patients with refractory epilepsy. DBF is placed against the inner aspect of the cheek, where it adheres, dissolves, and releases diazepam onto the buccal mucosa.[11,17] Compared with rectally administered diazepam, DBF has been shown to have a more consistent and predictable pharmacokinetic profile.[18,19]

In studies conducted to date, single doses of DBF 5 mg to 17.5 mg have been shown to be well tolerated in healthy adults and in adults with epilepsy.[11,18,20] Here, we report interim data from an ongoing study (NCT03428360) assessing the safety, tolerability, and usability of DBF administered by patients or caregivers in outpatient settings.

**Key Points**

- DBF is a novel formulation of diazepam intended to treat seizure emergencies in patients with refractory epilepsy
- This study assessed the safety, tolerability, and usability of self- or caregiver-administered DBF in people with epilepsy
- DBF was ultimately successfully placed on nearly all (98.6%) use occasions and readily used without difficulty by patients and caregivers
- Chronic/intermittent administration of DBF is well tolerated, and patient self- and/or caregiver administration of DBF is easily achieved
- Administration of a single dose of DBF was not followed by a second administration within 24 hours on 91.5% of use occasions

## 2 | MATERIALS AND METHODS

This phase 3, multicenter, open-label, long-term safety and tolerability study was initiated on January 23, 2018 at 22 sites in the USA. The study protocol, all protocol amendments, and informed consent forms were approved by an appropriately constituted institutional review board at each study site. The study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and all relevant regulations set forth in Title 21 of the Code of Federal Regulations. Prior to participating in any study-related activities, all participants were required to provide written consent after having been informed about the nature, duration, and purpose of the study and participation/withdrawal conditions.

### 2.1 | Study population

Eligible patients included male and female adults (age = 17-65 years), adolescents (age = 12-16 years), and children (age = 2-11 years) with an established diagnosis of epilepsy with motor seizures and clear alteration of awareness. Eligible participants required benzodiazepine treatment for bouts of increased seizures, which could include acute repetitive seizures or cluster seizures, occurring at least once monthly, on average, and were required to be on ≥1 concomitant antiepileptic medication at screening.

Patients were ineligible to participate in the study if they had a history of clinically significant gastrointestinal, renal/genitourinary, hepatic, hematologic, dermatologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other clinically significant abnormalities that could, in the opinion of the investigator, interfere with study procedures or jeopardize patient safety. Patients were also excluded if they had a significant traumatic injury, major surgery, or open biopsy within 30 days prior to screening; a recent history of suicidality; or clinically significant abnormal electrocardiogram findings. Female patients were required to have a negative serum and urine pregnancy test at screening, and females of childbearing potential were required to use an acceptable form of birth control for the duration of the study and for 30 days after study completion. Patients 17 years old or older were excluded if they had a positive screening for human immunodeficiency virus, hepatitis B surface antigen, hepatitis C, drugs of abuse, or alcohol.

## 2.2 | Study design

Patients were screened for eligibility within 1 to 28 days prior to study entry. Electronic diaries were used to document seizures, DBF use, adverse events (AEs), and changes in concomitant medication. For each patient, the study lasted at least 6 months and included four planned study site visits (Figure 1). At the baseline visit (study day 1), participants and caregivers were trained by the study team to administer DBF and use the electronic study diary. During training, study staff ensured that patients and caregivers understood the guidelines on when to use DBF, how to store DBF, how to open DBF packaging and successfully administer DBF as per detailed written instructions for use (Appendix S1), and how to record (in patient diaries) information related to patient seizure events, DBF administration and use, AEs, changes in patient health status, and changes in or additions to concomitant medications. These procedures were reviewed at all subsequent study visits and contacts. Study site visits were scheduled every 90 ± 14 days over the treatment course (≥6 months). A study site visit was also mandated within 14 days after first DBF use.

Dosing regimens were derived from population pharmacokinetic modeling of the existing weight-based dosing regimen for DRG, adjusting for differing pharmacokinetics, administration routes, and other factors. Initial dose was determined first by age group and then by body weight within each age group. At each site visit, the patient was weighed, and the investigator could use the patient's age, weight, and initial clinical response to adjust the dispensed DBF dose up or down by 2.5 mg. Dose options were 5, 7.5, 10, 12.5, 15, and 17.5 mg (Table S1).

Study participants and caregivers were instructed to administer DBF as acute seizure rescue for any at-home seizure episodes ordinarily treated with a benzodiazepine. If required, a second dose of DBF could be given within 4 to 12 hours after the first dose. No more than one seizure episode every 5 days and no more than five seizure episodes per month were to be treated with DBF or with any other product containing diazepam, except as instructed by a physician. Throughout the study, patients' baseline antiepileptic medication regimens could be adjusted in accordance with standard clinical practice.

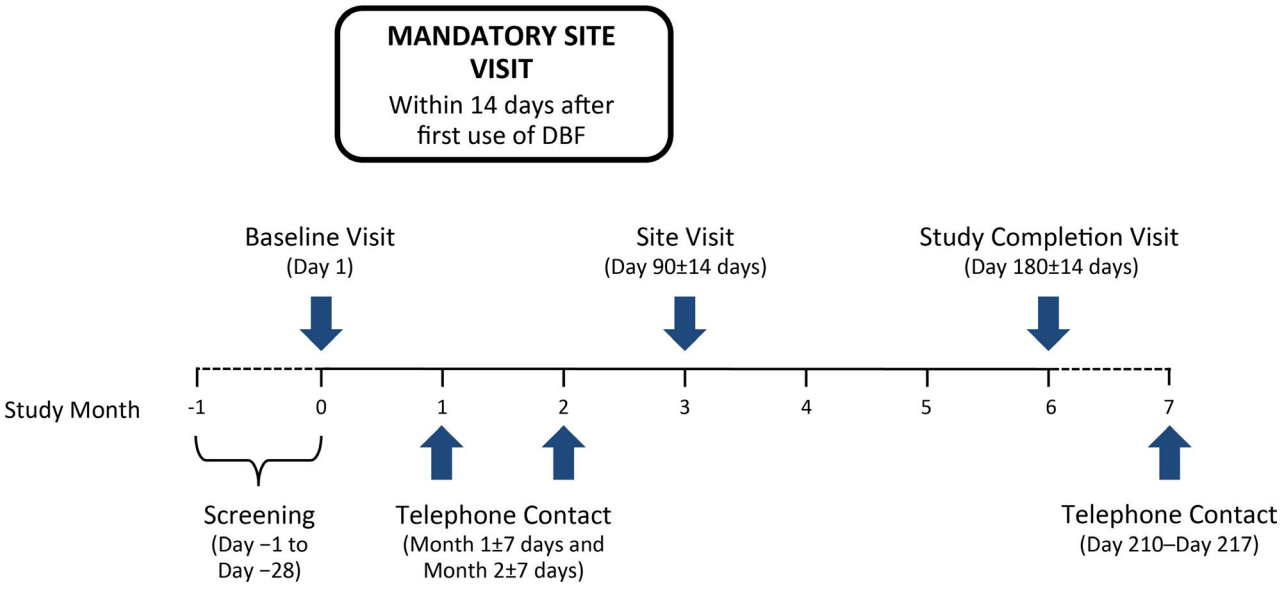


**FIGURE 1** Study schema. DBF, diazepam buccal film

### 2.3 | Assessment of DBF safety and tolerability

The primary study objective was to assess the safety and tolerability of DBF administered ≥3 times during the 6-month study period. At each study visit, safety was assessed by a trained investigator or study nurse. AEs were recorded throughout the treatment course and for up to 30 days after final administration of study drug, or until all drug-related toxicities resolved, whichever was later. Serious AEs were defined as events that are life-threatening or fatal, that result in hospitalization, or that caused persistent or significant incapacity or disruption of normal functioning.

The intensity of each AE was classified as mild (easily tolerated and minimally interfering with everyday activities), moderate (discomforting enough to interfere with everyday activities), or severe (preventing everyday activities). AEs were also classified by the investigator as probably, possibly, unlikely, or not related to study drug. AEs in the "probably" or "possibly" categories were considered treatment-related.

### 2.4 | Assessment of DBF usability

A secondary study objective was to evaluate DBF usability, defined as the patient and caregiver ability to administer DBF according to the instructions for use. The usability variables recorded after each use of DBF included buccal placement, oral cavity retention, and ability to open the packaging and remove the DBF. Successful buccal placement was defined as placement of the study drug against the buccal mucosa. Examples of unsuccessful oral cavity retention include swallowing the study drug before it can adhere to the inner cheek, and spitting out or blowing away the study drug after placement.

### 2.5 | Data analysis

Study sample size estimates were based on practical rather than statistical considerations, with a targeted minimum enrollment of 100 patients with epilepsy. The safety population included all patients who received ≥1 dose of DBF. All data were summarized with descriptive statistics generated with SAS version 9.3 or higher (SAS Institute). No formal statistical testing was planned.

## 3 | RESULTS

### 3.1 | Patients

As of January 31, 2020, 138 patients were enrolled in the study. Of these, 118 patients ranging in age from 4 to 62 years (82 adults, 19 adolescents, 17 children) have used DBF at least once and were included in the safety population. Of these patients, 72 (61.0%) remain actively enrolled, 29 (24.6%) completed the study, and 17 (14.4%) withdrew. Reasons for withdrawal include withdrawal by patient (n = 3), withdrawal of informed consent (n = 3), loss to follow-up (n = 2), noncompliance with study drug (n = 2), death (n = 2), physician decision (n = 1), adverse event (n = 1), and other reasons (n = 1); the reason for withdrawal was not captured for two patients.

As of the January 31, 2020 cutoff for this analysis, the mean (standard deviation [SD]) duration of study enrollment was 243.1 (161.2) days, and the mean (SD) number of DBF doses administered to each patient was 11.6 (13.6), with a

**TABLE 1** Patient demographic and baseline characteristics (safety population)

| Characteristic | Adult, n = 82 | Adolescent, n = 19 | Pediatric, n = 17 |
|---|---|---|---|
| Age, y | | | |
| Mean (SD) | 31.8 (10.6) | 14.3 (1.5) | 8.2 (2.5) |
| Sex, n (%) | | | |
| Female | 39 (47.6) | 12 (63.2) | 9 (52.9) |
| Male | 43 (52.4) | 7 (36.8) | 8 (47.1) |
| Race, n (%) | | | |
| White | 61 (74.4) | 14 (73.7) | 13 (76.5) |
| Black or African American | 6 (7.3) | 3 (15.8) | 2 (11.8) |
| Asian | 4 (4.9) | 1 (5.3) | 0 |
| Native Hawaiian or other Pacific Islander | 6 (7.3) | 0 | 0 |
| Other[a] | 5 (6.1) | 1 (5.3) | 2 (11.8) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 17 (20.7) | 4 (21.1) | 5 (29.4) |
| Not Hispanic or Latino | 63 (76.8) | 15 (78.9) | 12 (70.6) |
| Unknown | 2 (2.4) | 0 | 0 |
| Height, cm | | | |
| Mean (SD) | 165.1 (13.8)[b] | 155.2 (16.2) | 125.8 (17.0) |
| Weight, kg | | | |
| Mean (SD) | 73.2 (22.5) | 49.5 (11.6) | 28.0 (8.6) |
| Body mass index, kg/m$^2$ | | | |
| Mean (SD) | 26.6 (6.7) | 20.5 (3.4) | 17.4 (2.9) |

Abbreviation: SD, standard deviation.

[a]Not white, black or African American, native Hawaiian or other Pacific Islander, or American Indian or Alaska native.

[b]n = 81.

median (range) of 6.5 (1-79) doses. Patient demographic and baseline characteristics are listed in Table 1. Concomitant antiepileptic drugs, including benzodiazepine medications used for maintenance and rescue, are summarized in Table S2.

### 3.2 | DBF safety and tolerability

Table 2 provides an overview of the AEs reported to date. Overall, 22 serious AEs were reported by 17 (14.4%) patients. Of all the serious AEs, only one event of respiratory failure was considered "possibly" related to the study drug. Serious AEs included five epilepsy-related events (three events of increased seizure activity, one event of worsening seizure frequency, one event of worsening focal onset epilepsy), three aspiration events, two events of respiratory failure, three deaths (one sudden unexplained death in epilepsy, one death resulting from a malignant brain neoplasm, and one other death), and one case each of small bowel obstruction, enterocolitis, hypokalemia, intractable nausea, emesis, wrist dislocation, rufinamide toxicity, pneumonitis, and pneumonia. Treatment-related AEs occurred in nine (7.6%) patients (six adult, two adolescent, one pediatric). No patients discontinued participation in the study due to a treatment-related AE. Eight of the treatment-related AEs were mild, two were moderate, and one was severe, and all except the serious AE of respiratory failure noted above resolved without sequelae. There was one case each of mild local buccal discomfort, buccal swelling, and cheek skin sensitivity reported; each of these events resolved within 1 day. There were no reports of injury related to the administration of DBF to the oral mucosa.

AEs reported with a frequency of ≥2% in the entire study population are listed in Table 3. The most frequently reported AE was seizure; a total of 54 seizure events were reported in 21 (17.8%) patients.

### 3.3 | DBF usability

Of the 118 patients, 102 (86.4%) reported DBF usability data. All 102 patients had first-attempt administration success on ≥1 use occasion. Among these patients, there were 1087 DBF total use occasions, with a mean (SD) of 10.9 (12.2) administrations per patient. DBF was administered ictally (during a clinically observed seizure) or peri-ictally (within 5 minutes of seizure cessation) on 538 of 1087 (49.5%) use occasions. Timing of DBF administration across all 1087 use occasions is summarized in Table 4. Information on seizure type was available for 70.8% (770/1087) of the DBF use occasions. Seizure types were classified as follows: primary generalized tonic-clonic convulsion (36.9% [284/770] of use occasions), complex partial seizure (33.0% [254/770] of use occasions), secondary generalized tonic-clonic convulsion (11.7% [90/770] of use occasions), myoclonic seizure (10.9% [84/770] of use occasions), simple partial seizure (6.5% [50/770] of use occasions), absence seizure (1.0% [8/770] of use occasions). DBF was successfully administered on 98.6% (1072/1087) of use occasions, with 93.3% (1014/1087) successful on the first attempt, 3.3% (36/1087) on the second attempt, and 2.0% (22/1087) on the third or a subsequent attempt. Attempts on 15 of 1087 (1.4%) use occasions were unsuccessful; in six of the 15 occasions where buccal placement was unsuccessful, the film was still ingested by the patient.

Table 5 summarizes the reasons for unsuccessful DBF placement reported for the unsuccessful use occasions. Notably, there were only two (0.2%) occasions of unsuccessful placement attributable to swallowing the DBF before it adhered to the buccal mucosa. Patients and caregivers reported no difficulty removing the DBF from the foil pouch on nearly all (96.3% [1047/1087]) use occasions.

Self-administration was attempted on 188 of 795 (23.6%) of use occasions by adults. Among the 74 adults who reported usability data, 27 (36.5%) had at least one occasion of self-administration; among these 27 patients, self-administration occurred on 62.0% (188/303) of use occasions.

Most (91.5% [995/1087]) bouts of increased seizure activity were successfully managed with a single dose of DBF within 24 hours, with a second dose of DBF being required within 24 hours in 8.5% (92/1087) of use occasions.

## 4 | DISCUSSION

Prompt action is required to treat cluster seizures to reduce recurrence, progression to status epilepticus, and brain damage.[7,21] Benzodiazepines have been extensively studied and are considered first-line pharmacologic treatment options for seizure emergencies[14]; they are also generally well tolerated in this setting.[22,23] Despite the known efficacy and safety of treatment with benzodiazepines, many patients with epilepsy do not have a prescription for seizure rescue medication on hand. A recent observational study reported by Detyniecki and colleagues showed that only 28% of patients with recent history of cluster seizures reported having a prescription for rescue medication.[24] Another survey study, conducted by Penovich and colleagues to assess patient awareness of cluster seizure risks and treatment benefits, showed that only 20% of adult patients with cluster seizures reported taking a rescue medication in seizure emergencies.[4] This treatment gap may be reflective of the need for more convenient, patient-friendly pharmacologic treatment options for seizure rescue.

**TABLE 2** Summary of adverse events (safety population, N = 118)

| Parameter | Adult, n = 82 | Adolescent, n = 19 | Pediatric, n = 17 | Total, N = 118 |
|---|---|---|---|---|
| Number (%) of patients, number of events | | | | |
| Any AE | 48 (58.5), 187 | 16 (84.2), 38 | 11 (64.7), 27 | 75 (63.6), 252 |
| Any serious AE | 10 (12.2), 15 | 4 (21.1), 4 | 3 (17.6), 3 | 17 (14.4), 22 |
| Any severe AE | 8 (9.8), 17 | 1 (5.3), 1 | 3 (17.6), 3 | 12 (10.2), 21 |
| Discontinuation due to AE | 0 | 0 | 0 | 0 |
| Death | 2 (2.4), 2 | 1 (5.3), 1 | 0 | 3 (2.5), 3 |
| Any treatment-related AE[a] | 6 (7.3), 8 | 2 (10.5), 2 | 1 (5.9), 1 | 9 (7.6), 11 |
| Specific treatment-related AEs[b] | | | | |
| Fatigue | 1 (1.2), 1 | 1 (5.2), 1 | 0 | 2 (1.7), 2 |
| Somnolence | 2 (2.4), 2 | 0 | 0 | 2 (1.7), 2 |
| Lethargy | 1 (1.2), 1 | 0 | 0 | 1 (0.8), 1 |
| Altered state of consciousness | 1 (1.2), 1 | 0 | 0 | 1 (0.8), 1 |
| Mouth swelling | 0 | 1 (5.2), 1 | 0 | 1 (0.8), 1 |
| Oral discomfort | 1 (1.2), 1 | 0 | 0 | 1 (0.8), 1 |
| Gait disturbance | 1 (1.2), 1 | 0 | 0 | 1 (0.8), 1 |
| Skin sensitization | 1 (1.2), 1 | 0 | 0 | 1 (0.8), 1 |
| Respiratory failure | 0 | 0 | 1 (5.8), 1[c] | 1 (0.8), 1 |

Abbreviation: AE, adverse event.

[a]Defined as AE categorized as having "possible" or "probable" relationship to study drug.

[b]Of the 11 reported treatment-related AEs, eight were mild, two were moderate, and one was severe.

[c]This was a serious AE.

Ideal characteristics for a seizure rescue medication include rapid absorption and onset of action, portability, easy preparation and administration, sustained activity, and a favorable safety profile.[9,25] As noted previously, currently available treatment options for seizure rescue are not feasible to use or accepted by many patients. Considerable progress has been made to develop alternative pharmacologic treatments, such as DBF, that will meet varied patient and caregiver preferences and needs for portability and ease of use.

Diazepam buccal film has a predictable and consistent pharmacokinetic profile in the management of seizure emergencies.[17,18,20] Interim results from this safety and tolerability study indicate that DBF has been generally well tolerated in this population of adult, adolescent, and pediatric patients with epilepsy. To date, treatment-related AEs have been relatively uncommon with DBF, and the vast majority (72.7%) of reported treatment-related AEs have been mild in severity. There were no reports of injury during the administration of DBF in the current study, and only three cases of mild local discomfort or sensitivity associated with DBF were observed; all three quickly resolved without sequelae and without dose interruption.

The relatively low incidence of somnolence in this study (4.2%) and in an earlier study of DBF bioavailability (5.7%)[26] is noteworthy because somnolence is the most frequently observed AE in patients with epilepsy treated with DRG (23%).[27] Potential reasons for this difference in observed rates of somnolence may be related to differences in patient populations, severity of epilepsy, seizure types, and/or concomitant antiepileptic medications across studies.

The usability assessments in the current study showed that both patients and caregivers administered DBF without difficulty. Also, DBF was successfully placed on 98.6% of use occasions, and patients ultimately received their dose of DBF on 1078 (99.2%) use occasions. Overall, the DBF dose was administered during the ictal or peri-ictal period in about one-half (49.5% [538/1087]) of the use occasions. As per the patient- and caregiver-reported usability data, DBF appears efficacious in the current study, as seizure rescue was achieved with just a single dose of DBF in the vast majority (91.5% [995/1087]) of use occasions. Also, a meaningful

**TABLE 3** Adverse events reported in >2% of the safety population

| Adverse event | Overall population, N = 118[a] | |
|---|---|---|
| | Patients, n (%) | Events, n |
| Seizure | 21 (17.8) | 54 |
| Upper respiratory tract infection | 7 (5.9) | 7 |
| Nausea | 5 (4.2) | 5 |
| Pyrexia | 5 (4.2) | 5 |
| Somnolence | 5 (4.2) | 5 |
| Vomiting | 5 (4.2) | 6 |
| Cough | 4 (3.4) | 5 |
| Fall | 4 (3.4) | 5 |
| Lethargy | 4 (3.4) | 5 |
| Skin abrasion | 4 (3.4) | 5 |
| Weight decreased | 4 (3.4) | 6 |
| Weight increased | 4 (3.4) | 5 |
| Dizziness | 3 (2.5) | 3 |
| Headache | 3 (2.5) | 3 |
| Otitis media | 3 (2.5) | 3 |

[a]Nine patients experienced a total of 11 treatment-related adverse events.

**TABLE 4** Timing of administrations of DBF (safety population)

| Timing of DBF administration in relation to seizure event | Use occasions (N = 1087),[a] n (%) |
|---|---|
| 1 h before seizure to 5 min before seizure | 37 (3.4) |
| 5 min before seizure to start of seizure | 66 (6.1) |
| Start of seizure to 5 min after seizure | 538 (49.5) |
| >5 min after seizure to 30 min after seizure | 297 (27.3) |
| >30 min after seizure | 111 (10.2) |
| Data not captured | 38 (3.5) |

Abbreviation: DBF, diazepam buccal film.

[a]Use occasions for which usability data were available.

**TABLE 5** Reported reasons for unsuccessful DBF placement attempts (safety population)

| Reason | Unsuccessful attempts based on 1087 use occasions,[a] n (%)[b] |
|---|---|
| Clenching jaw/will not open mouth | 27 (2.5) |
| Excessive drooling | 24 (2.2) |
| Spit out DBF before it adhered to buccal mucosa | 23 (2.1) |
| Swallowed DBF before it adhered to buccal mucosa | 2 (0.2) |
| Other (none of the above) | 33 (3.0) |

Abbreviation: DBF, diazepam buccal film.

[a]Use occasions for which usability data were available.

[b]Respondents could choose >1 reason for an unsuccessful placement attempt.

proportion of adult patients' DBF uses were self-administered (23.6% [188/795] of use occasions).

In addition to demonstrating generally favorable safety, tolerability, and usability profiles, DBF may have some potential advantages over rectal and intranasal formulations of diazepam. It has been reported that most patients and caregivers prefer nonrectal methods of administering seizure rescue medications.[3,14,16,28-31] Rectal administration, which typically requires disrobing, may be embarrassing for both patient and caregiver, and legal and social circumstances may restrict its use.[11] Intranasal drug administration can be challenging when attempted under ictal conditions; it may be associated with unpredictable absorption and increase aspiration risk[9]; and it may be poorly accepted by patients.[32] Packaging for both rectal and intranasal formulations is relatively large and bulky, which reduces product portability. The small, thin DBF film can be easily transported and is easily removed from its packaging and affixed to the buccal mucosa inside the cheek, which may facilitate patient compliance.[11]

Data from phase 1 studies in healthy adults have shown that DBF exhibits near-linear, dose-proportional pharmacokinetics over a dose range of 5-15 mg, whereas maximum plasma concentration is less than dose-proportional with DRG.[18-20] Also, the pharmacokinetics of DBF was shown to be comparable when administered under interictal and ictal/peri-ictal conditions in adults with epilepsy.[26]

Our study has several limitations. Most of the data collected were from adult patients; our study had a relatively small sample size of pediatric and adolescent patients, from whom we continue to accrue DBF safety and usability data. In addition, given the subjective and observational nature of the electronic diary data collected,[33] reporting of seizures by patients and/or caregivers may be unreliable. The absence of a control makes it difficult to definitively establish whether AEs were related to film application, to the effect of diazepam, or to other factors such as concomitant seizure activity.

In conclusion, interim results from this ongoing observational study indicate that DBF is safe and well tolerated with chronic intermittent administration and use in this population of adult, adolescent, and pediatric patients with epilepsy who experienced seizure emergencies. The small size and packaging of DBF allow for easy transport of the rescue medication. Adult patients experiencing a seizure emergency can readily self-administer DBF; in addition, a caregiver can administer the medication for the patient. In the vast majority (91.5%) of use occasions, a single dose of DBF was sufficient to successfully manage the cluster seizure.

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## DISCLOSURES

S.S. is a member of the speaker bureau for LivaNova and has served as a consultant for Aquestive Therapeutics, Inc. M.A.G. has received research support from Aquestive Therapeutics, Inc., Cerevel, Engage Therapeutics, UCB, Biogen, Eisai, LivaNova, Otsuka Pharmaceutical, and SK Pharma. A.H.H. has served as a paid consultant to Aquestive Therapeutics, Inc. C.B. and G.S. are employees of Aquestive Therapeutics, Inc.

## ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## DATA AVAILABILITY STATEMENT

Aquestive Therapeutics, Inc. will not be sharing individual deidentified participant data or other relevant study documents.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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