CROSSOVER STUDY EVALUATING THE EFFECT OF SEIZURES ON THE ABSORPTION OF DIAZEPAM FROM A BUCCAL FILM FORMULATION IN CHILDREN WITH EPILEPSY

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INTRODUCTION

- Diazepam, a benzodiazepine, is an accepted treatment for seizure emergencies, including acute repetitive seizures (ARS).[1, 2, 3]
- Diazepam buccal film (DBF) is a novel dosage form of diazepam intended for the treatment of ARS that is compact, portable and easily administered.[1]
- At time of use, DBF is placed onto the buccal mucosa inside the cheek where it adheres firmly and then rapidly dissolves, delivering diazepam transbucally and via the gastric route.[1]
- In adults, DBF was demonstrated to exhibit reliable and predictable dose-proportional pharmacokinetics (PK) for both maximal plasma diazepam concentration (C_{max}) and plasma exposure (area under the plasma drug concentration-time curve [AUC]).[4]
- A prior crossover study in adults with epilepsy demonstrated comparable diazepam PK when DBF was delivered within 5 min of a seizure (periictal administration) as when administered at other times (interictal administration).[4]
- In this study, we examined DBF in children with epilepsy, addressing usability and tolerability and investigating if diazepam absorption is influenced by administration in proximity to an impaired awareness seizure.

OBJECTIVES

- To compare plasma exposures from DBF administered in pediatric subjects with epilepsy under periictal or interictal conditions.
- To evaluate the safety/tolerability of DBF in pediatric subjects with epilepsy.
- To evaluate the usability of DBF in pediatric subjects with epilepsy.

METHODS

- DBF was administered in a range of doses from 5 mg to 17.5 mg (based on the age and weight of the subject). The same dose was administered in Treatment Period A and Treatment Period B.
- Blood was collected immediately prior to dosing (0 time) and over the subsequent 4 hours for analysis of DBF plasma concentrations.

STUDY DESIGN

- This was a multicenter, open-label, crossover study in which subjects received DBF in the interictal state (Treatment Period A) or during the ictal/periictal state (Treatment Period B).
- DBF was administered by an HCP and subjects were observed until the film was dissolved.
- Some subjects received both treatments. The minimum period between dosing was 14 days.

KEY INCLUSION CRITERIA

- Healthy adult males and females aged 2 to 16 years, inclusive.
- Subjects had a body weight of ≥6 kg and ≤111 kg.

METHODS (cont'd)

KEY INCLUSION CRITERIA (cont'd)

- Subjects had a clinical diagnosis of epilepsy, were receiving at least one antiepileptic medication, and were scheduled for admission to an epilepsy monitoring unit, general clinical research center, or similar facility for evaluation.
- Subjects had an average frequency of ≥1 clinically apparent seizures every 3 days or ≥10 clinically apparent seizures per month, with alteration of consciousness.

RESULTS

SUBJECTS

- 24 subjects enrolled in the study received at least one dose of DBF: 17 subjects were dosed in the interictal period,16 subjects dosed in the periictal period, and 9 subjects dosed in both periods. PK data presented includes measurements from all subjects including those that were dosed in only 1 period.
- Subjects were analyzed in groups based on age: 2-5 (n=6), 6-11 (n=9) and 12-16 (n=9).

PHARMACOKINETICS

- Diazepam exhibited PK profiles similar to that previously observed in adults in all pediatric age groups studied.
- Substantial variability in PK parameters was observed from subject to subject and between dosing period for those subjects who received 2 treatments.
- No consistent trends or differences in diazepam C_{max} or AUC were observed between Period A and Period B in the 3 age groups (**Figure 1**, **Figure 2**, and **Figure 3**).
- Diazepam T_{max} values were similar for subjects dosed in Period A and Period B (data not shown).
- Including all treatment periods for all age groups, the geometric LSM C_{max} in Period B was less than that in Period A, but the difference was not statistically significant (**Table 1**).
- From the AUC comparisons, both time profiles demonstrated higher AUC values in Period A compared with Period B. This difference was statistically significant for the 0-to-4-hour profile, but not for the 0-to-2-hour profile.

SAFETY AND TOLERABILITY

- No trend with age category, dose, or period was observed.
- Of the 24 treated subjects, 12 (50.0%) subjects had at least 1 TEAE.
- Overall, 2 (8.3%) subjects had TEAEs that were considered possibly or probably related to DBF (1 subject had mild vomiting and 1 subject had mild dizziness).
- Of the total 40 TEAEs, the majority (31 TEAEs) were mild in severity.
- Two subjects had serious TEAEs (1 subject had a severe seizure cluster and 2 episodes of severe pneumonia, and 1 subject had a moderate seizure).
- No subject died during the study and no TEAE led to DBF discontinuation.

RESULTS (cont'd)

Figure 1: Mean (±SD) Diazepam Plasma Concentration for Age Group 2 to 5 Years (Linear Scale) (PK Population)

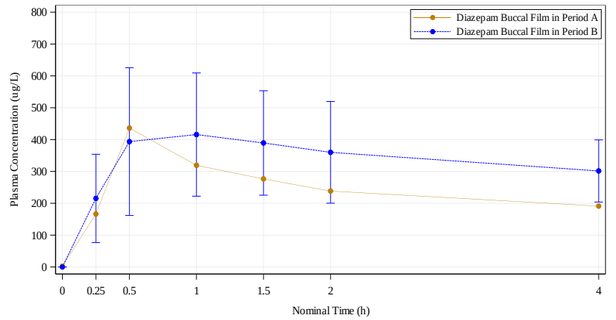


Figure 2: Mean (±SD) Diazepam Plasma Concentration for Age Group 6 to 11 Years (Linear Scale) (PK Population)

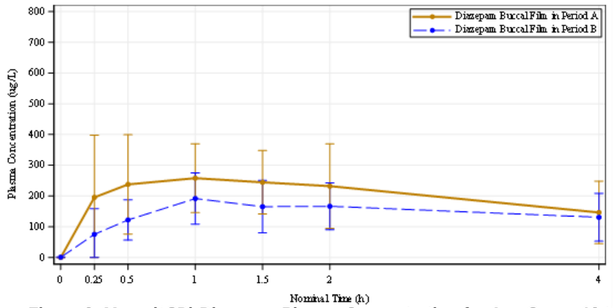
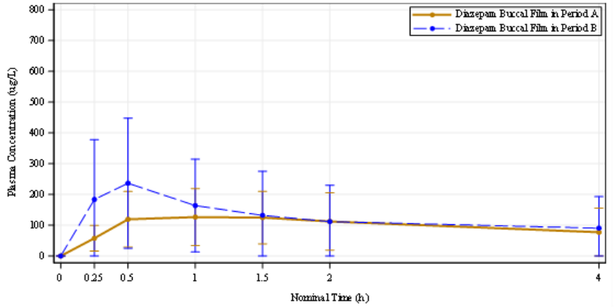


Figure 3: Mean (±SD) Diazepam Plasma Concentration for Age Group 12 to 16 Years (Linear Scale) (PK Population)



RESULTS (cont'd)

Table 1: LSM Comparisons of Diazepam PK Parameters Between Periods (PK Population for all age groups combined)

Parameter (unit)	n	Geometric LSM Period A	Geometric LSM Period B	Ratio (%)	90% Geometric CI (%) Lower	90% Geometric CI (%) Upper	P Value	Intra-subject CV (%)
AUC_{0-2h} (h*ng/mL)	8	356.02	262.35	73.69	56.08	96.82	0.0278	29.43
AUC_{0-4h} (h*ng/mL)	8	678.45	492.75	72.63	58.35	90.40	0.0278	23.41
C_{max} (ng/mL)	8	267.87	206.23	76.99	57.06	103.87	0.1420	32.42

Note: Ratios are calculated as Period B ÷ Period A.

DISCUSSION

- When DBF was administered to children within 5 min of an impaired awareness seizure, absorption of diazepam occurred to a similar extent as when administered at other times.
- DBF was safe and well tolerated in children as young as 2 years of age.
- No evidence of local buccal mucosal irritation or TEAEs related to the application of DBF were reported.
- DBF was successfully placed and generally used correctly in both the interictal and ictal/periictal states.

CONCLUSIONS

- DBF provides a convenient way to deliver diazepam for the treatment of acute repetitive seizure emergencies in children.

REFERENCES

1. Rogawski MA, Heller AH. Diazepam buccal film for the treatment of acute seizures. *Epilepsy Behav.* 2019;101(Pt B):106537. doi:10.1016/j.yebeh.2019.106537
2. Heller AH, et al. *Neurology*. 2018;90(15 suppl):P4.272. http://n.neurology.org/content/90/15_Supplement/P4.272.
3. Heller AH, et al. *Neurology*. 2018;90(15 suppl):P4.273. http://n.neurology.org/content/90/15_Supplement/P4.273.
4. Rogawski MA, Gong H, Liow K, Aboumatar S, Klein P, Gelfand MA, Jung C, Wargacki S, Mehta R, Heller AH. Pharmacokinetics of diazepam buccal soluble film in adult patients with epilepsy: comparison of bioavailability with periictal and interictal administration (Abstract 2.453), American Epilepsy Society Annual Meeting, 2018.

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DISCLOSURES

Dr. Slatko is a paid consultant to Aquestive Therapeutics, Inc.
Dr. Rogawski has previously served as a paid consultant to Aquestive Therapeutics, Inc. but was not compensated for work on this project.
Dr. Wargacki is an employee of Aquestive Therapeutics.