

Oral Soluble Film Products for Epilepsy: Clobazam (COSF) and Diazepam (DBSF)

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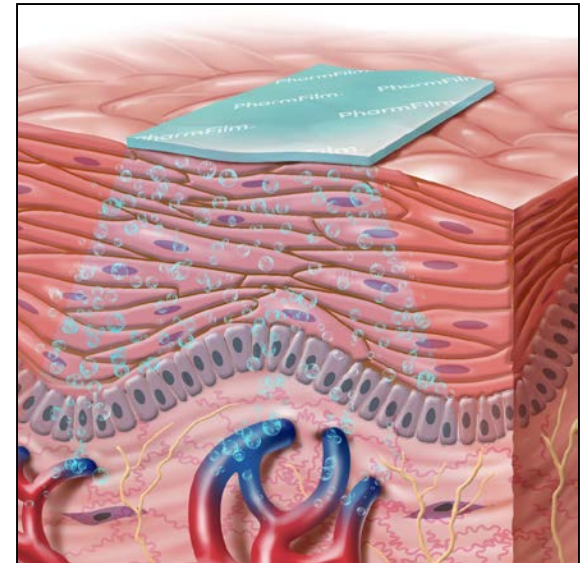
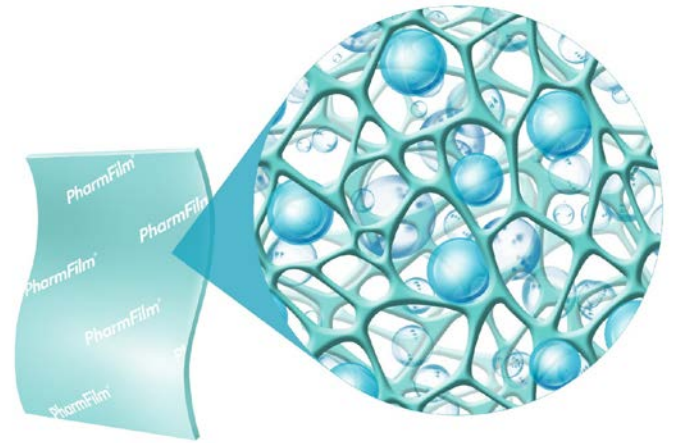


Conflict of Interest

- Dr. Rogawski serves as a paid consultant for Aquestive Therapeutics.
- Dr. Rogawski is currently or has previously served as consultant to other companies developing technology for similar applications, including Upsher-Smith Laboratories and Epalex Corporation.

How Does PharmFilm Work?

- Polymers are used as film formers to hold API and excipients in place
- Patented techniques are used to ensure the API is uniformly distributed throughout the film
- pH modifiers and permeation enhancers cause transport across the buccal mucosa
- Begins to dissolve immediately on application to mucosa
- API released from buccal film is absorbed by the transmucosal route and is also swallowed



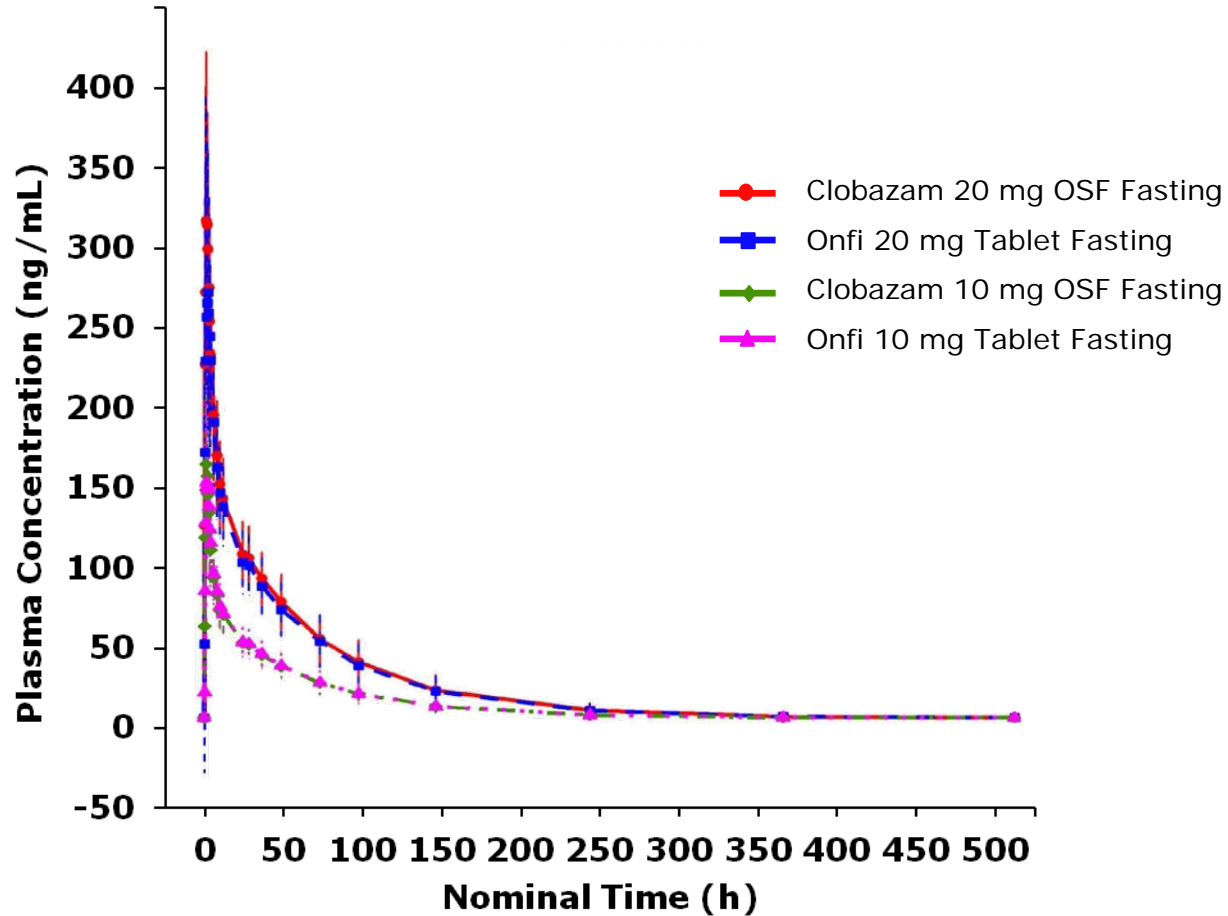
Clobazam Oral Soluble Film (COSF)

- An new alternative clobazam dosage form for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients aged 2 years and older (outside the United States for anxiety disorders and epilepsy)
- May be easier for some caregivers to administer than oral tablets or oral liquid suspension
- Demonstrates capability of film technology

Bioequivalence Study of COSF (162018)

- **Open-label, randomized, single-dose, 4-period, 4-arm, crossover, comparative bioavailability study**
- **Healthy, nonsmoking male and female volunteers (N=51)**
- **Treatments**
 - COSF 10 mg (N=47)
 - COSF 20 mg (N=45)
 - Onfi[®] (clobazam) Tablet 10 mg (N=47)
 - Onfi[®] (clobazam) Tablet 20 mg (N=47)
- **Washout:** 28 days between dosing
- **Blood sampling time points:**
 - 0.333, 0.667, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 28, 36, 48, 72, 96, 144, 240, 360, and 504 hours postdose in each period
- **Safety:** vital signs, physical exam, clinical labs, adverse events

Mean Plasma Concentration Profiles: COSF vs Onfi[®] (Study 162018)



Data on file, Aquestive Therapeutics.

20 mg Bioequivalence (Study 162018)

Bioequivalence of Clobazam Oral Soluble Film 20 mg vs Onfi[®] Tablets 20 mg – PK Population (N=45)

Parameter	Least-Squares Geometric Means		Ratio of Geo Means ¹ (%)	90% Geometric CI ²	
	COSF 20 mg	Onfi 20 mg		Lower	Upper
AUC _{0-t} (ng·h/mL)	10531.45	10152.24	103.74	101.32	106.21
AUC _{0-inf} (ng·h/mL)	10712.10	10344.68	103.55	101.16	106.00
C _{max} (ng/mL)	386.59	376.84	102.59	95.43	110.28

¹Calculated using least-squares means according to formula $e^{(\text{Difference})} \times 100$.

²90% geometric confidence interval using ln-transformed data.

Data on file, Aquestive Therapeutics.

10 mg Bioequivalence (Study 162018)

Bioequivalence of Clobazam Oral Soluble Film 10 mg vs Onfi[®] Tablets 10 mg – PK Population (N=47)

Parameter	Least-Squares Geometric Means		Ratio of Geo Means ¹ (%)	90% Geometric CI (%) ²	
	COSF 10 mg	Onfi 10 mg		Lower	Upper
AUC _{0-t} (ng·h/mL)	4554.83	4583.30	99.38	96.81	102.02
AUC _{0-inf} (ng·h/mL)	4714.55	4759.87	99.05	96.72	101.43
C _{max} (ng/mL)	179.96	188.53	95.45	90.19	101.03

¹Calculated using least-squares means according to formula $e^{(\text{Difference})} \times 100$.

²90% geometric confidence interval using ln-transformed data.

Data on file, Aquestive Therapeutics.

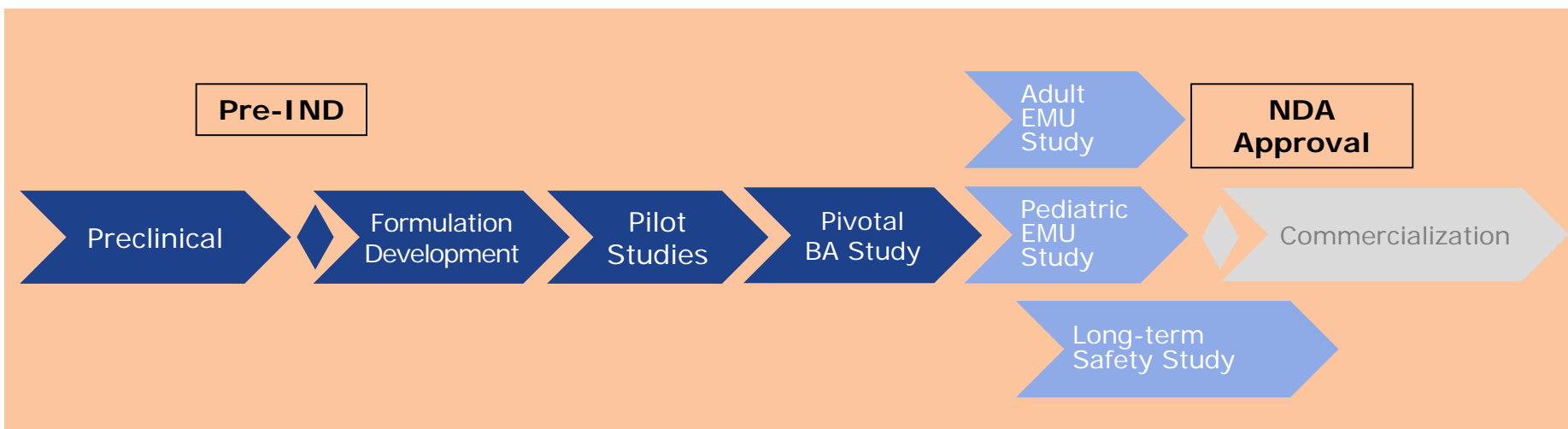
Conclusions for COSF Bioequivalence Study (Study 162018)

- COSF 20 mg is bioequivalent to Onfi[®] 20 mg
- COSF 10 mg is bioequivalent to Onfi[®] 10 mg
- T_{\max} values for COSF were comparable to those for Onfi
- COSF is dose proportional over the 10-20 mg range
- COSF at doses of 10 and 20 mg was safe and well tolerated

Diazepam Buccal Soluble Film (DBSF)

- An alternative to Diastat® AcuDial™ (diazepam rectal gel) for the treatment of acute repetitive seizures (seizure clusters)

DBSF Received FDA Fast Track Designation



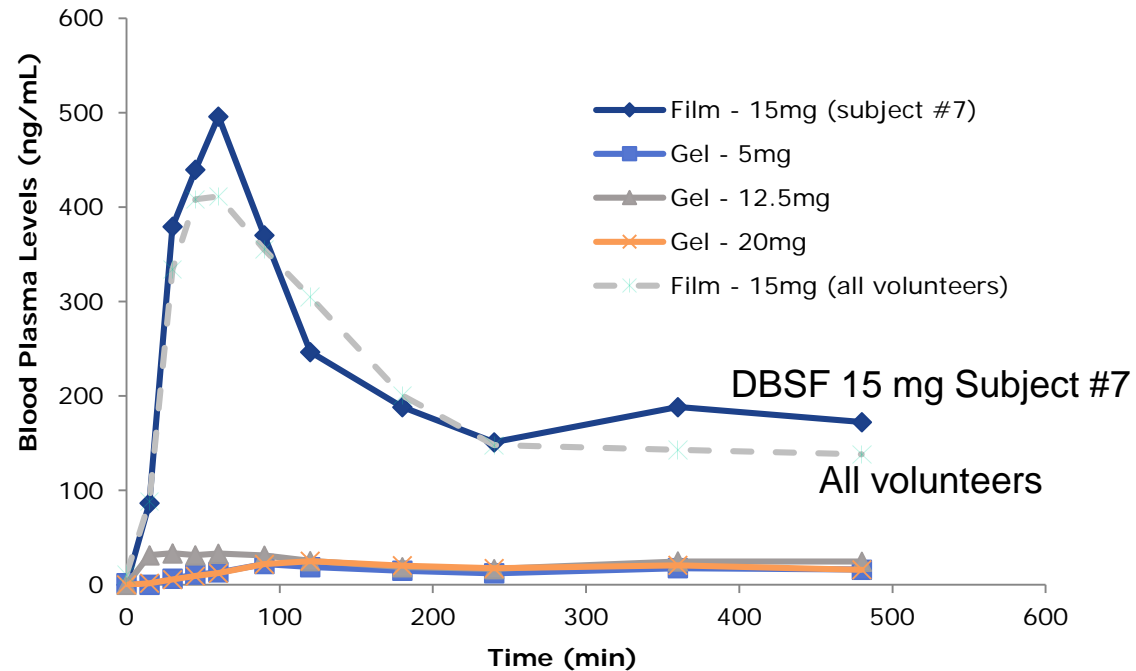
- Fast track designation with option for rolling submission
- Expected NDA filings via 505(b)(2) pathway in early 2018

■ Completed Development Step ■ Ongoing Development Step ■ Future Development Step

DBSF: No 'PK Non-Responders'

- Diastat in some subjects did not produce expected plasma concentrations of diazepam
- In studies to date, DBSF has exhibited consistent plasma diazepam concentrations – including those subjects who did not obtain expected diazepam levels with Diastat

DBSF Pivotal Pharmacokinetics vs Diastat® AcuDial™ Rectal Gel¹ – Individual Subject

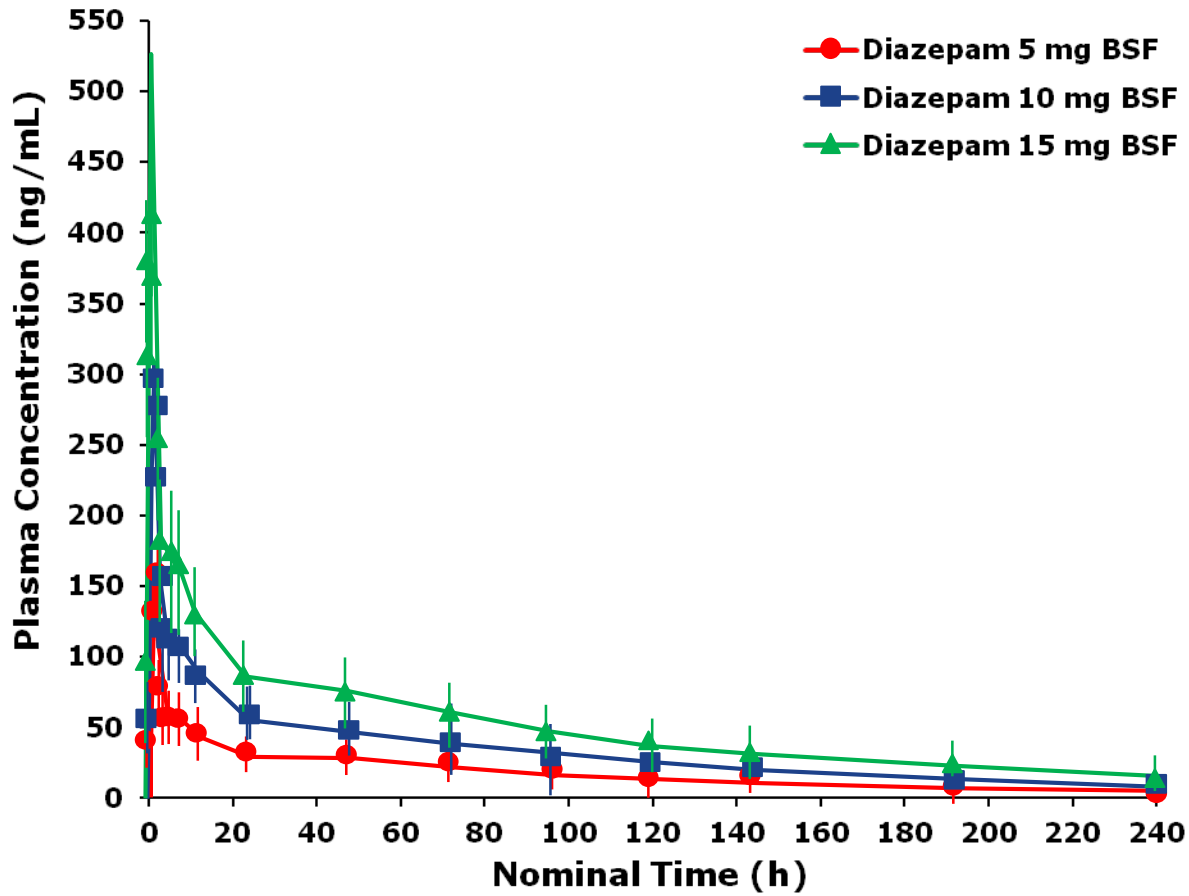


¹Fasted conditions

Completed Human PK Studies with DBSF

- Bioavailability of DBSF 5 mg and Diastat® AcuDial™ 5 mg Rectal Gel (Study 1899)
 - Bioavailability of DBSF 20 mg and Diastat® AcuDial™ 20 mg Rectal Gel (Study 1900)
 - Dose Proportionality of DBSF 5, 10, 15 mg (Study 162013)
 - Bioavailability of DBSF 15 mg vs Diastat® AcuDial™ 5, 12.5, and 20 mg Rectal Gel (Study 162921)
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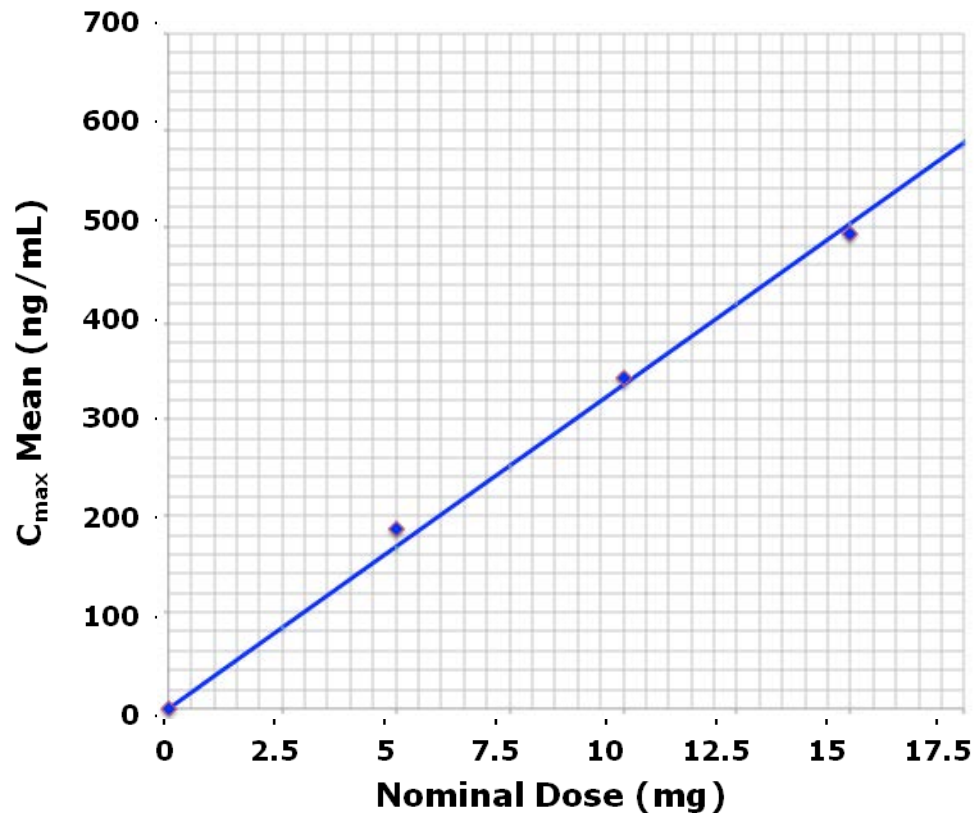
Geometric Mean Diazepam Plasma Concentrations (Linear Scale) (Study 162013)



Data on file, Aquestive Therapeutics.

Dose Proportionality (C_{\max}) (Study 162013)

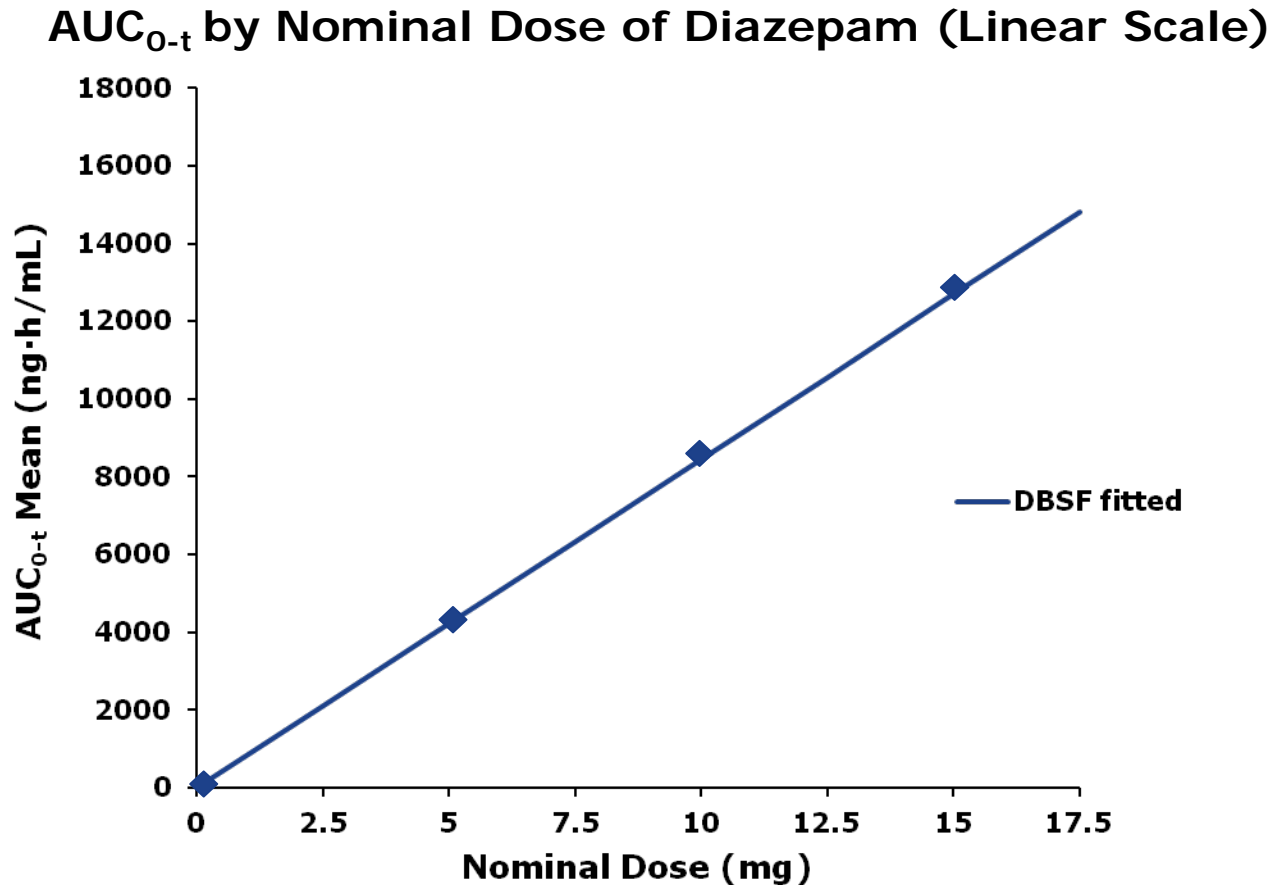
C_{\max} by Nominal Dose of Diazepam (Linear Scale)



C_{\max} values were dose proportional.
DBSF: Diazepam 5, 10, 15 mg Buccal Soluble Film.

Data on file, Aquestive Therapeutics.

Dose Proportionality (AUC_{0-t}) (Study 162013)



AUC_{0-t} values were dose proportional.

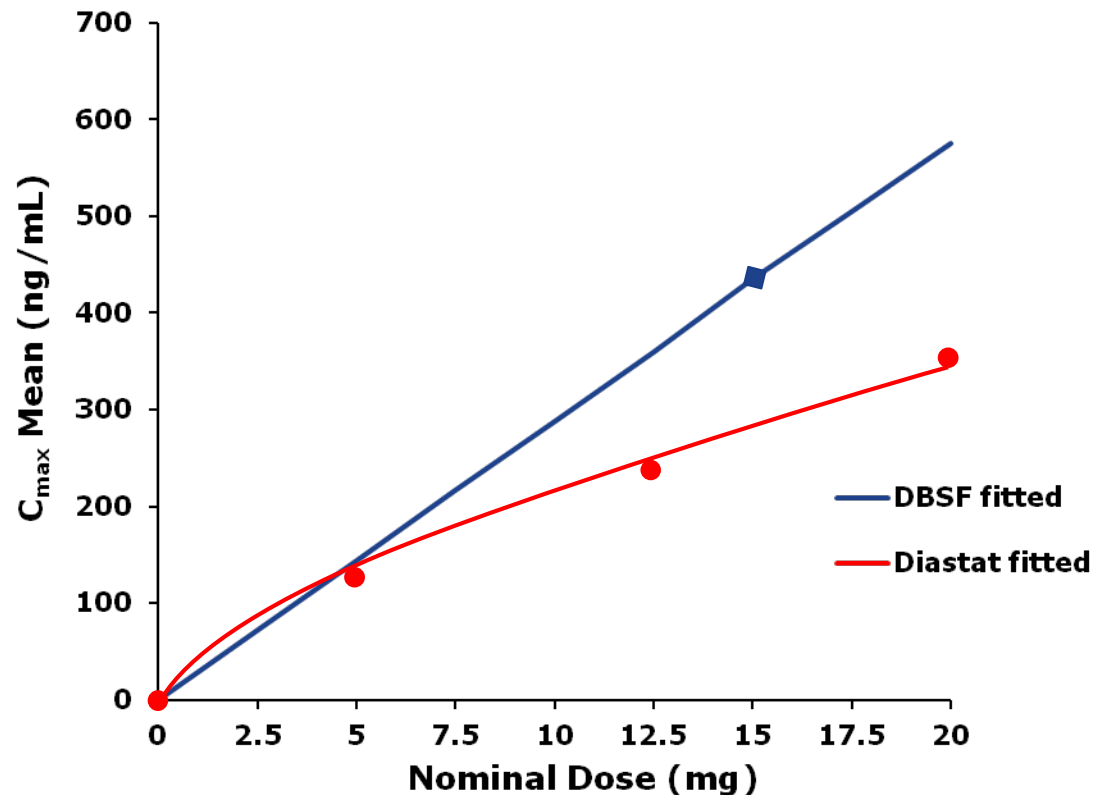
DBSF: Diazepam 5, 10, 15 mg Buccal Soluble Film.

Data on file, Aquestive Therapeutics.

Relative Bioavailability (Study 162021)

C_{max} by Nominal Dose of Diazepam (Linear Scale)

- **DBSF**
 C_{max} is known to be dose proportional
- **Diastat[®] AcuDial[™]**
 C_{max} values were less than dose proportional



DBSF: Diazepam 15 mg Buccal Soluble Film.

Diastat AcuDial: Diazepam 5 mg (1 mL of 10 mg/2 mL), 12.5 mg (2.5 mL of 20 mg/4 mL), and 20 mg (4 mL of 20 mg/4 mL) rectal gel.

Data on file, Aquestive Therapeutics.

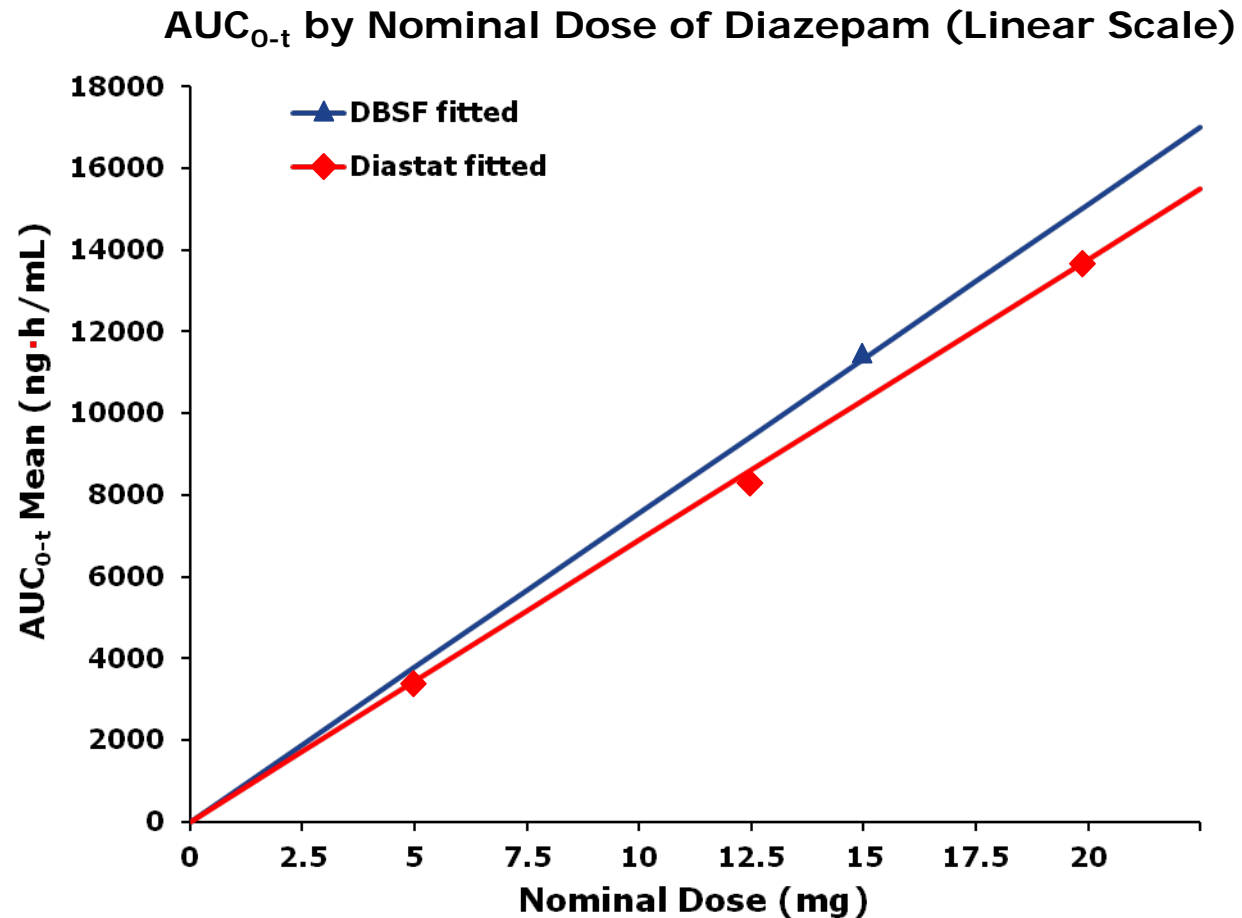
Relative Bioavailability (Study 162021)

- **DBSF**

DBSF is known to be dose proportional for AUC

- **Diastat[®] AcuDial[™]**

Diastat is dose proportional for AUC



DBSF: Diazepam 15 mg Buccal Soluble Film.

Diastat AcuDial: Diazepam 5 mg (1 mL of 10 mg/2 mL), 12.5 mg (2.5 mL of 20 mg/4 mL), and 20 mg (4 mL of 20 mg/4 mL) rectal gel.

Data on file, Aquestive Therapeutics.

Proposed DBSF Dosing: Dose of DBSF in mg Equivalent to Dose of Diastat[®] AcuDial[™] in mg

Diastat Dose (mg)	Protocol-Specified DBSF Dose ¹ (mg)
5	5
7.5	7.5
10	7.5
12.5	10
15	12.5
17.5	12.5
20	12.5

¹Dose of DBSF expected to provide C_{max} equal to C_{max} for Diastat dose.

Data on file, Aquestive Therapeutics.

PK Features of DBSF vs Diastat[®] AcuDial[™]

- Dose-proportional kinetics
- Less intersubject variability
- No bioavailability failures

T_{\max} (h)

Dose (mg)	DBSF	Diastat [®] AcuDial [™]
5	0.81	0.50
10	0.999	
12.5		1
15	1.9–1.27	
20		1.5

DBSF Studies Ongoing

- Adult EMU Study
 - Pediatric EMU Study
 - Long-term Safety Study
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The End
