SUBLINGUAL EPINEPHRINE FILM'S MUCOADHESIVE PROPERTIES ENSURE CONSISTENT ORAL PLACEMENT AND DRUG RELEASE

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INTRODUCTION

- Epinephrine administered intramuscularly into the anterolateral thigh via manual injection or auto-injector (e.g., EpiPen®, Auvi-Q®) is currently the first-line treatment for anaphylaxis.[1]
- The two injection methods have distinct pharmacokinetic (PK) profiles,[2] but both clinically stabilize a patient with anaphylaxis in the outpatient or hospital setting.
- AQST-109 (also referred to as DESF) is a novel prodrug of epinephrine delivered via sublingual film and is being developed for the emergency treatment of type 1 allergic reactions, including anaphylaxis.
- AQST-109 could be conveniently carried by patients (e.g., in a wallet, pocket, small purse, or on the back of a mobile phone).
- The potential impact of placement or movement of AQST-109 was not previously assessed.

OBJECTIVES

- The study objectives were to compare the PK of epinephrine following single administration of AQST-109 to that following single administration of epinephrine intramuscular (IM) injection in healthy adult subjects.
- To evaluate the safety and tolerability of epinephrine following single administration of AQST-109 to that following single administration of epinephrine IM injection in healthy adult subjects.
- Subsequent analysis was conducted to evaluate the impact of intraoral film placement and movement on variability in PK and pharmacodynamics (PD).

METHODS

STUDY DESIGN

- An open-label, single-center, randomized, four-period, four-treatment, four-sequence, comparative PK study.
- During the studies, subjects received:
  - AQST-109 12 mg
  - Epinephrine 0.3 mg via IM injection
  - Epinephrine 0.3 mg via EpiPen
  - Epinephrine 0.3 mg via Auvi-Q

METHODS (cont'd)

KEY INCLUSION CRITERIA

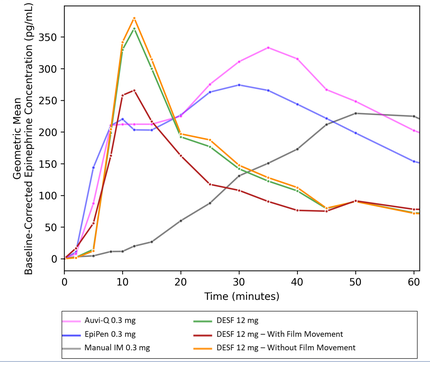
- Healthy adult males and females aged 18 to 55 years.
- Body mass index (BMI) between 18 and 30 kg/m^2.
- Weight ≥45 kg for females and ≥50 kg for males.

RESULTS

PK DATA

- Movement was noted in 12.5% of subjects (8 of 64) .
- DESF delivery resulted in epinephrine PK comparable to Epinephrine Auto-Injectors (EAIs) or IM injection, and remained consistent independent of variations in film location, defined by change in location upon mouth checks (Figure 1).
- When movement was noted, there were no significant differences between subjects with or without film movement.
- Geometric mean (GM) C_{max}
  - 351.14 pg/mL with film movement and 490.27 pg/mL without film movement; p = 0.49
- Median T_{max}
  - 12 minutes with film movement and 12 minutes without film movement; p = 0.96

Figure 1: Geometric Mean Epinephrine Concentration over Time By Treatment



RESULTS (cont'd)

Table 1: Epinephrine PK Parameters With and Without Film Movement

Parameter[a]	With Film Movement (N=8)	Without Film Movement (N=56)
T_{max}, min	12	12
C_{max}, pg/mL	351.14 (93.57%)	490.27 (84.4%)
$AUC_{0\text{-}10}$, h·pg/mL	16.92	17.72
$AUC_{0\text{-}20}$, h·pg/mL	57.14	73.83
$AUC_{0\text{-}30}$, h·pg/mL	79.31	108.99
$AUC_{0\text{-}45}$, h·pg/mL	102.31	144.79

[a] Geometric mean values except for median T_{max}. C_{max} also reports coefficient of variation (%).

PD DATA

- DESF PD remained consistent independent of small variations in film location, as shown in Figures 2 and 3. {PR not shown}.
- There were no significant differences in median change in systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse rate (PR) between subjects with or without film movement (Table 2).
- Additionally, there were no significant differences in median max SBP, DBP or PR between the two subgroups (Table 2).

Table 2: Epinephrine PD Parameters With and Without Film Movement

Parameter[b]	With Film Movement	Without Film Movement
SBP		
Change, mmHg	7.75	6.50
Max, mmHg	143.50	132.50
DBP		
Change, mmHg	3.25	1.50
Max, mmHg	88.50	80.00
Pulse		
Change, beats/min	2.00	3.25
Max, beats/min	87.50	84.00

[b] all values are median

RESULTS (cont'd)

Figure 2: Median Change from Baseline in Systolic Blood Pressure

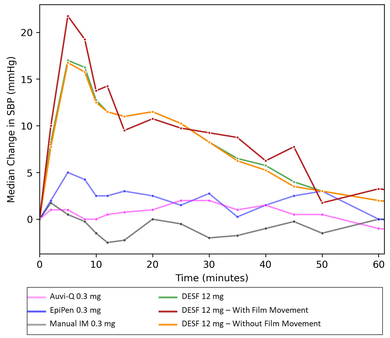
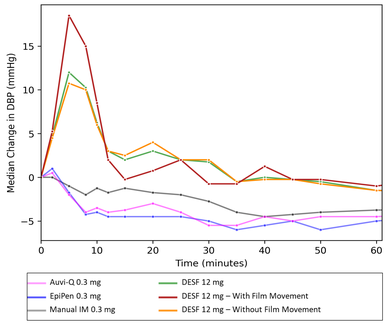


Figure 3: Median Change from Baseline in Diastolic Blood Pressure



SAFETY AND TOLERABILITY

- Most adverse events were consistent with known physiologic effects of epinephrine and were similar across treatments.
- There were no severe treatment-emergent adverse events (TEAEs) reported.
- All reported TEAEs were mild, transient, or resolved with minimal intervention.

CONCLUSIONS

- **Analysis of residual film location between 1.5 to 3 minutes post-administration revealed minimal displacement**
  - **87.5% of subjects had no change in film location between timepoints**
- **The initial placement or subsequent movement of the sublingual film had no impact on epinephrine PK or PD, with all results comparable to injection.**
- **Similar to all prior studies to date, AQST-109 was safe and well tolerated at the therapeutic dose.**
- **These results suggest AQST-109 offers a consistent, robust and permissive method of drug delivery in anaphylaxis management**

REFERENCES

1. Shaker MS, Wallace DV, Golden DBK, et al. *J Allergy Clin Immunol.* 2020;145(4):1082-1123.
2. Worm M, Nguyen D, Rackley R, et al. *Clin Transl Allergy.* 2020;10:21.

ACKNOWLEDGMENTS

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DISCLOSURES

Drs. Golden, Greenhawt, Lieberman, Bernstein, and Oppenheimer are members of the advisory board and consultants to Aquestive Therapeutics, Inc. Drs. Kraus and Wargacki are employees of Aquestive Therapeutics.