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PHARMACOKINETICS AND PHARMACODYNAMICS OF EPINEPHRINE SUBLINGUAL FILM VERSUS INTRA-MUSCULAR EPINEPHRINE

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INTRODUCTION

- Epinephrine administered intramuscularly (IM) into the anterolateral thigh is the first-line treatment for anaphylaxis.[1]
- However, epinephrine—particularly epinephrine auto-injectors (eg, EpiPen)—is underutilized due to various factors, including needle phobia, delayed administration, and failure to carry.[2,3]
- A different treatment modality could help address these isuses.[3,4]
- AQST-109 (also called DESF), a novel prodrug of epinephrine delivered via sublingual film, is being developed for the emergency treatment of type 1 allergic reactions.
- AQST-109 is easily carried (eg, in a wallet, pocket, or small purse) and can be quickly administered by placing the film under the tongue and allowing it to dissolve in the saliva.
- The objective of this study was to compare epinephrine pharmacokinetics (PK) and pharmacodynamics (PD) following administration via sublingual film (AQST-109) or IM injection.

METHODS

STUDY DESIGN

- EPIPHAST is a phase 1, open-label, three-part adaptive design crossover study in healthy adult volunteers.
- In Part 2 of EPIPHAST, participants were randomized to receive 4 doses of epinephrine in one of two sequences (**Figure 1**):

Figure 1: Dosing schedule for EPIPHAST Part 2

	Period 1	Period 2	Period 3	Period 4
Sequence 1	AQST-109 12 mg	Epinephrine IM 0.3 mg	AQST-109 12 mg	Epinephrine IM 0.3 mg
Sequence 2	Epinephrine IM 0.3 mg	AQST-109 12 mg	Epinephrine IM 0.3 mg	AQST-109 12 mg

- There was a washout period of ≥24 hours between dosing periods 1 and 2 and between dosing periods 3 and 4. The washout period between dosing periods 2 and 3 was at least 3 days.
- All dosing occurred while participants were in the clinical research unit.
- All doses were administered by the clinic staff under fasting conditions.
- Doses were administered at the same time each day (±30 mins).

METHODS (cont'd)

KEY INCLUSION CRITERIA

- Healthy adult males and non-pregnant, non-lactating females aged 18 to 50 years with a body mass index (BMI) between 18 and 30 kg/m^2.
- Non-smoker/non-vaper for at least 3 months prior to screening.
- Participant and/or their partner uses a highly effective method of contraception/birth control.
- Systolic blood pressure (SBP) 95 to 140 mmHg, diastolic blood pressure (DBP) 55 to 90 mmHg, oxygen saturation ≥95% O_2, and pulse 50 to 100 beats/min.

DATA COLLECTION

- Plasma samples were collected for 8 hours post-dose and used to calculate PK parameters, including maximum concentration (C_{max}), time to C_{max} (T_{max}) and area under the curve (AUC).
- PD parameters included SBP, DBP, and pulse.

SAFETY

- Continuous cardiac monitoring was performed for at least 1 hour prior to dosing and until at least 4 hours after dosing.
- Subjects were monitored for adverse events and local tolerability.

ENDPOINTS

- The primary endpoint was the comparison of baseline-corrected epinephrine PK parameters following administration via AQST-109 or IM injection.
- Secondary endpoints included comparisons of PD parameters.

ANALYSIS

- Statistical analyses were conducted after baseline correction.
- For the PK endpoints, a mixed scaling approach was used.
- Safety and tolerability data were reported using descriptive statistics.

RESULTS

DEMOGRAPHICS

- Twenty-four healthy adults (12 male, 12 female) were enrolled in EPIPHAST Part 2.
- Mean age was 41 years (range: 26 to 50 years).
- Twelve participants (50%) were White, 10 (42%) were Black or African American, and 2 (8%) were Asian.
- Five participants (21%) were Hispanic or Latino.
- Mean (SD) BMI was 26.0 (±2.8) kg/m^2.

RESULTS (cont'd)

PK DATA

- Compared with manual IM injection, AQST-109 had a faster T_{max} with comparable C_{max} and AUCs during the clinically relevant time frame for the acute treatment of anaphylaxis (**Figure 2** and **Table 1**).

Figure 2: Mean Epinephrine Concentration over Time

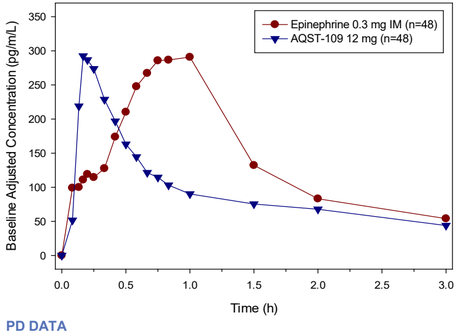


Table 1: Epinephrine PK Parameters

Parameter[a]	AQST-109 12 mg (n=48)	Epinephrine 0.3 mg IM (n=48)
T_{max}, min	15	50
C_{max}, pg/mL	274.3 (105.9)	350.6 (51.8)
AUC_{0-5}, h·pg/mL	1.2	3.0
AUC_{0-10}, h·pg/mL	7.9	9.4
AUC_{0-15}, h·pg/mL	20.9	15.2
AUC_{0-20}, h·pg/mL	33.1	23.0
AUC_{0-30}, h·pg/mL	56.7	47.5
$AUC_{0-\infty}$, h·pg/mL	362.3	538.6

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

PD DATA

- Early and robust changes in SBP (**Figure 3**) and DBP (**Figure 4**) were directionally opposite for AQST-109 (increased) and epinephrine IM (decreased).
- These average changes were consistent with individual profiles for AQST-109 (SBP and DBP) and for IM (DBP). However, for SBP after IM administration, the apparent decrease is an artifact of intrasubject variability and inconsistent timing/magnitude of response.
- Pulse rates were similar between AQST-109 and epinephrine IM and did not, on average, vary much from baseline (data not shown).

Figure 3: Mean Change from Baseline in Systolic Blood Pressure

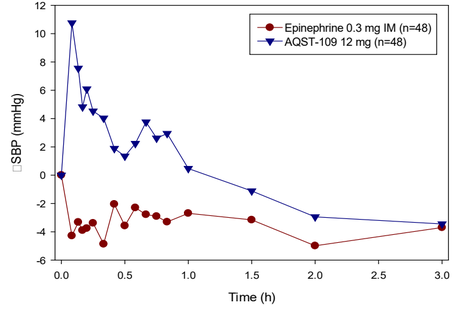
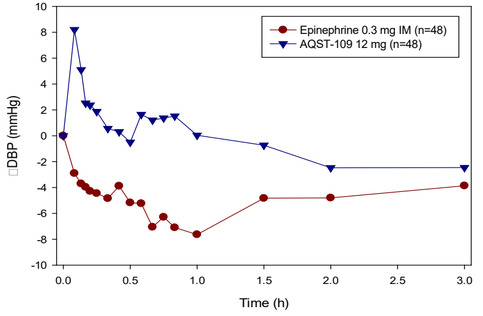


Figure 4: Mean Change from Baseline in Diastolic Blood Pressure



RESULTS (cont'd)

SAFETY and TOLERABILITY

- Most adverse events were consistent with known physiologic effects of epinephrine and were similar across treatments.
- In general, the reported treatment-emergent adverse events were mild (Grade 1), transient, and resolved with minimal intervention.

CONCLUSIONS

- **Epinephrine administered via AQST-109 reaches T_{max} in 15 minutes compared with 50 minutes for IM injection.**
- **Overall exposure to epinephrine was similar between AQST-109 and IM injection during the clinically relevant time frame (ie, 30 minutes) for the acute treatment of anaphylaxis.**
- **Administration of AQST-109 consistently resulted in early, robust increases in SBP and DBP.**
- **Preliminary work suggests that sublingual AQST-109 is a safe, alternative treatment that could address significant unmet needs in patients with anaphylaxis.**

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ACKNOWLEDGMENTS

This study was sponsored by Aquestive Therapeutics. Writing support was provided by Katherine A. DeBruin, PhD, of Kodiak Consulting Group, Inc. and funded by Aquestive Therapeutics.

DISCLOSURES

Drs. Golden, Oppenheimer, Carmargo, Greenhawt, Fleisher and Bernstein are members of the advisory board and consultants to Aquestive Therapeutics. Dr. Slatko is an employee of Aquestive Therapeutics.