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PHARMACOKINETICS OF EPINEPHRINE SUBLINGUAL FILM FOLLOWING THREE DIFFERENT ADMINISTRATION PROCEDURES

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INTRODUCTION

- Epinephrine is the cornerstone of anaphylaxis management, but epinephrine auto-injectors are often under-utilized due to various factors, including needle phobia, administration errors, and failure to carry.[1-3]
- A different treatment modality could address the significant unmet need resulting from deficiencies of auto-injectors and improve patient access and usage, leading to improved outcomes.[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—the same indication as epinephrine auto-injectors.
- 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 three different post-administration saliva hold times (ie, enforced periods in which participants refrain from swallowing).

METHODS

STUDY DESIGN

- EPIPHAST is a phase 1, open-label, three-part adaptive design crossover study in healthy adult volunteers.
- In three periods of EPIPHAST Part 3, participants received a single dose of AQST-109 12 mg using the following saliva hold times:
  - 4-min hold: hold the film and saliva in the sublingual (SL) space for 4 minutes, then swallow saliva
  - 2-min hold: hold the film and saliva in the SL space for 2 minutes, then swallow saliva
  - Free swallow: hold the film in SL space while swallowing saliva freely (no required saliva hold time)
- All participants received AQST-109 using all 3 saliva hold times. The order of administration procedures was randomized.
- 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).
- There was a washout period of at least 5-7 days between doses.

ENDPOINTS

- The primary endpoints were PK parameters compared across the 3 saliva hold times.
- Secondary endpoints were comparisons of PD parameters across the 3 saliva hold times.

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.

ANALYSIS

- Statistical analysis were conducted after baseline correction.
- Mixed-effects ANOVA models for a parallel design were used to analyze the natural log-transformed PK parameters.
- Safety and tolerability data were reported using descriptive statistics.

RESULTS

DEMOGRAPHICS

- Twenty-four healthy adults (12 male, 12 female) were enrolled in EPIPHAST Part 3.
- Mean age was 39 years (range: 18 to 50 years).
- Ten participants (42%) were White, 9 (38%) were Black or African American, and 5 (21%) were Asian.
- Five participants (21%) were Hispanic or Latino.
- Mean BMI was 25 kg/m^2.

ADMINSTRATION

- All subjects completed all saliva hold times without difficulty.

RESULTS (cont'd)

PK DATA

- All 3 saliva hold times yielded very rapid peaks in epinephrine concentrations, with similar T_{max} values (**Figure 1** and **Table 1**).

Figure 1: Mean Epinephrine Concentration over Time by Saliva Hold Times (AQST-109 12 mg)

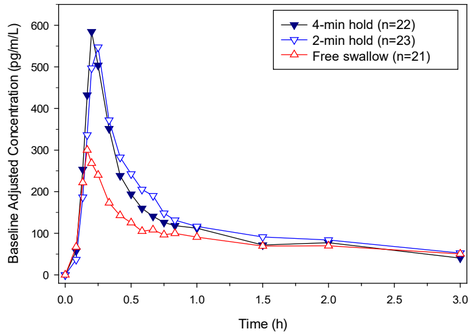


Table 1: Epinephrine PK Parameters by Saliva Hold Time (AQST-109 12 mg)

Parameter[a]	4-min hold (n=22)	2-min hold (n=23)	Free Swallow (n=21)
T_{max}, min	12	15	15
C_{max}, pg/mL	350.4 (177.6)	303.9 (164.1)	211.2 (135.5)
AUC_{0-5}, h·pg/mL	1.5	0.9	1.8
AUC_{0-10}, h·pg/mL	12.8	9.5	9.4
AUC_{0-15}, h·pg/mL	33.3	27.5	20.5
AUC_{0-20}, h·pg/mL	51.2	45.7	20.5
AUC_{0-30}, h·pg/mL	79.1	75.1	49.8
AUC_{0-t}, h·pg/mL	411.5	435.4	340.4

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

RESULTS (cont'd)

PD DATA

- The early and robust increases in SBP (**Figure 2**), DBP (**Figure 3**), and pulse (**Figure 4**) are similar regardless of administration procedure.

Figure 2: Mean Change from Baseline in Systolic Blood Pressure

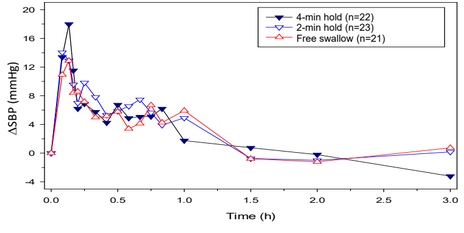


Figure 3: Mean Change from Baseline in Diastolic Blood Pressure

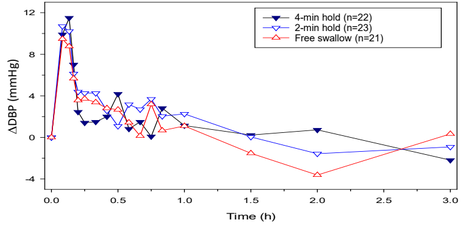
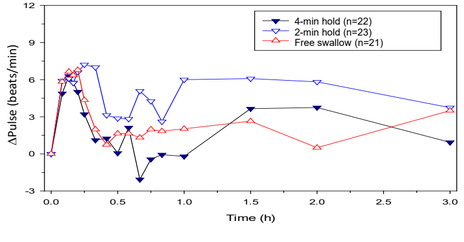


Figure 4: Mean Change from Baseline in Pulse



RESULTS (cont'd)

SAFETY and TOLERABILITY

- Most adverse events were consistent with known physiologic effects of epinephrine and were similar across treatments.
- There were no significant treatment-emergent adverse events (Grade 3 TEAEs) reported.
- In general, the reported TEAEs were mild (Grade 1), transient, and resolved with minimal intervention.

CONCLUSIONS

- **All 3 administration procedures (4-min hold, 2-min hold, and free swallow) produced rapid and clinically relevant epinephrine exposures and similar PD responses.**
- **There was little incremental benefit to holding saliva in the mouth for longer than 2 minutes.**
- **While the 2-minute hold time produced higher C_{max} and AUC values than allowing participants to swallow freely, there was little impact on the PD responses.**
- **AQST-109 delivers clinically meaningful epinephrine exposure regardless of whether saliva is held in the mouth after administration or swallowed freely.**

REFERENCES

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