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IMPACT OF FOOD EXPOSURE ON THE PHARMACOKINETICS OF EPINEPHRINE SUBLINGUAL FILM

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INTRODUCTION

- Food is among most common causes of anaphylaxis, and symptoms can occur quickly after ingestion.[1]
- Prompt treatment is essential, and guidelines recommend intramuscular injections of epinephrine as the first-line therapy for anaphylaxis.[2]
- AQST-109 (also called DESF), a novel prodrug of epinephrine delivered via sublingual film, is being developed for the emergency treatment of anaphylaxis.
- 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.
- Since the epinephrine prodrug in AQST-109 is absorbed sublingually, it is important to assess its PK/PD when administered immediately following food ingestion.
- Of particular interest is the effect of sticky foods, such as peanut butter.
- Therefore, the objective of this study was to compare epinephrine PK/PD when dosed under fasted conditions versus immediately following the ingestion of a peanut butter sandwich.

METHODS

STUDY DESIGN

- EPIPHAST is a phase 1, open-label, three-part adaptive design crossover study in healthy adult volunteers.
- In one period of EPIPHAST Part 3, participants received a single dose of AQST-109 12 mg immediately after eating a peanut butter sandwich.
- The results were compared with AQST-109 12 mg when no food was given.
- In both scenarios, the film and the saliva were held in the sublingual (SL) space for 4 minutes before the saliva was swallowed.
- 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.

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.

METHODS (cont'd)

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 epinephrine PK parameters in the presence and absence of oral food residue.
- Secondary endpoints were comparisons of PD parameters in the presence and absence of oral food residue.

ANALYSIS

- Statistical analysis were conducted after baseline correction.
- Mixed-effects ANOVA models 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.

RESULTS (cont'd)

PK DATA

- T_{max} was comparable (12 min with or without oral food residue; **Figure 1**).
- C_{max} [coefficient of variation] was slightly lower with oral food residue (285.7 [116.9]) than with no food (350.4 [177.6]).
- AUCs were similar at all time points through 30 minutes (**Figure 2**).

Figure 1: Mean Epinephrine Concentration over Time (AQST-109 12 mg)

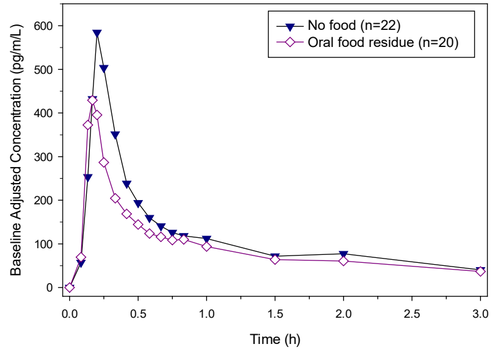
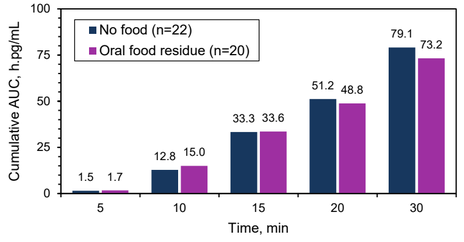


Figure 2: Cumulative Area Under the Curve over Time (AQST-109 12 mg)



- AUC_{0-t} (duration of study) was 411.5 h·pg/mL with no food and 341.7 h·pg/mL with oral food residue.

RESULTS (cont'd)

PD DATA

- Following administration of AQST-109, there was an early and robust increase in SBP (**Figure 3**), DBP (data not shown), and pulse (**Figure 4**), regardless of food intake.
- Over time, all PD parameters returned to expected baseline values.
  - Post-prandial SBP and DBP are known to be lower than fasting values because of increased blood flow to the gut.

Figure 3: Change from Baseline in Systolic Blood Pressure over Time (AQST-109 12 mg)

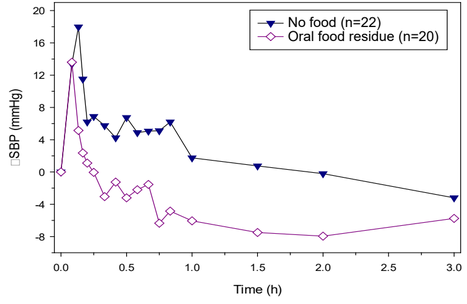
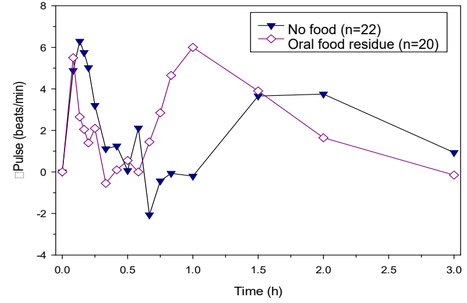


Figure 4: Change from Baseline in Pulse over Time (AQST-109 12 mg)



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

- **T_{max}, C_{max}, and AUCs through 30 minutes after administration of AQST-109 were consistent in the presence or absence of oral food residue.**
- **Oral food residue did not meaningfully affect the post-administration increases in PD parameters, which are desirable in the setting of acute treatment of anaphylaxis.**
- **This study provides reassurance that epinephrine absorption from AQST-109 would not be impaired in "real-world" situations if the product is used to treat an anaphylactic reaction during eating, even if the food is a sticky substance such as peanut butter.**

REFERENCES

1. American Academy of Allergy, Asthma and Immunology. Anaphylaxis. https://www.aaaai.org/tools-for-the-public/conditions-library/allergies/anaphylaxis. Accessed December 20, 2022.
2. Posner LS, Carmago Jr CA. *Drug Healthc Patient Safety*. 2017;9:9-18.

ACKNOWLEDGMENTS

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DISCLOSURES

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