L13

COMPARISON OF THE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES OF EPINEPHRINE DELIVERED BY A SUBLINGUALLY ABSORBED FILM VERSUS 0.3 MG ADMINISTERED BY A STANDARD IM INJECTION OR THE EPIPEN®

Matthew Greenhawt MD, MBA, MSc[1], John Oppenheimer MD[2], David Golden MD[3], Carlos A. Camargo Jr MD, DrPH[4], David Fleisher MD[1], David Bernstein MD[5], Jay Lieberman MD[6], Mark L. Freedman MD[7], Gary Slatko MD[8], Steve Wargacki PhD[8]

[1]Children's Hospital Colorado, [2]UMDNJ Rutgers University School of Medicine, [3]Medstar Franklin Square Hospital, [4]Massachusetts General Hospital/Harvard Medical School, [5]University of Cincinnati College of Medicine, [6]University of Tennessee Health Science Center, [7]Pharma Medica Research Inc., [8]Aquestive Therapeutics

INTRODUCTION

- Epinephrine administered intramuscularly into the anterolateral thigh via manual injection or auto-injector (eg, EpiPen®) is the first-line treatment for anaphylaxis.[1]
- The two injection methods have distinct pharmacokinetic (PK) profiles,[2] but both are able to effectively stabilize a patient with anaphylaxis until emergency services can arrive.
  - In the United States, >90% of the population can be reached by emergency services within 26 minutes of a 911 call for help.[3]
- 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, including 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.
- The objective of this study was to compare epinephrine PK and pharmacodynamics (PD) following single-dose administration of AQST-109 vs manual injection vs EpiPen.

METHODS

STUDY DESIGN

- EPIPHAST II is a phase 1, multi-period, open-label crossover study in healthy adult volunteers who received each of the following treatments:
  - AQST-109 12 mg
  - Epinephrine 0.3 mg via IM injection
  - Epinephrine 0.3 mg via EpiPen
- The order of AQST-109 and epinephrine IM injection was randomized; all participants were dosed with the EpiPen during the last treatment period.
- 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 (±2 hours).
- There was a washout period of at least 24 hours between AQST-109 and IM injection, and a washout period of approximately 7 days before EpiPen administration.

KEY INCLUSION CRITERIA

- Healthy, non-smoking males and females aged 18 to 50 years with a body mass index (BMI) between 18 and 30 kg/m^2.
- No use of tobacco or nicotine-containing products within 6 months prior to dosing.
- All participants with child-bearing potential had to be willing to use acceptable, effective methods of contraception.
- Systolic blood pressure (SBP) 95 to 140 mmHg, diastolic blood pressure (DBP) 55 to 90 mmHg, 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 after administration via AQST-109 vs manual IM injection.
- Secondary endpoints included comparisons of epinephrine PK parameters after administration via AQST-109 vs EpiPen and PD parameters.

ANALYSIS

- Statistical analysis were conducted after baseline correction.
- Mixed-effects ANOVA models with fixed effects for sequence, period, and treatment and a random effect for subject within sequence were used to analyze the natural log-transformed PK parameters (except T_{max}).
- Safety and tolerability data were reported using descriptive statistics.

RESULTS

Table 1: Demographics

	N=24
Female, n (%)	13 (54)
Mean age (range), years	35 (24–49)
Race, n (%)	
White	8 (33)
Asian	8 (33)
Black or African American	7 (29)
Multi-racial	1 (4)
Hispanic or Latino, n (%)	5 (21)
Mean BMI, kg/m^2	25

RESULTS (cont'd)

PK DATA

- Consistent with previous studies,[2] EpiPen produced a higher epinephrine C_{max} and shorter T_{max} than manual IM injection. However, AQST-109 yielded the fastest T_{max} among the 3 treatments (**Figure 1** and **Table 2**).[3]
- Epinephrine AUCs with AQST-109 were bracketed by the higher AUCs with EpiPen and the lower AUCs with IM manual injection over the critical period of up to 30 minutes prior to access to emergency services.

Figure 1: Mean Epinephrine Concentration over Time by Treatment

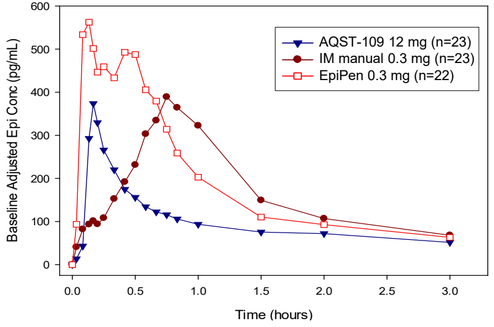


Table 2: Epinephrine PK Parameters by Treatment

Parameter[a]	AQST-109 (n=23)	IM Manual (n=23)	EpiPen (n=22)
T_{max}, min	12	45	23
C_{max}, pg/mL	294.0 (87.4)	411.2 (53.8)	744.2 (53.0)
AUC_{0-5}, h·pg/mL	1.1	2.6	8.4
AUC_{0-10}, h·pg/mL	12.9	7.4	41.4
AUC_{0-15}, h·pg/mL	29.6	13.5	75.3
AUC_{0-20}, h·pg/mL	44.7	21.6	110.0
AUC_{0-30}, h·pg/mL	70.2	51.2	185.5
AUC_{0-t}, h·pg/mL	385.5	680.2	725.4

[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 observed in SBP (**Figure 2**), DBP (**Figure 3**), and pulse (**Figure 4**) with AQST-109 reflect the faster T_{max} compared with IM manual injection and EpiPen.
- In the first few minutes after administration, SBP and DBP response—which are critical to stabilizing a patient with anaphylaxis—were strongest with AQST-109 despite the higher epinephrine C_{max} with EpiPen.

Figure 2: Mean Change from Baseline in Systolic Blood Pressure

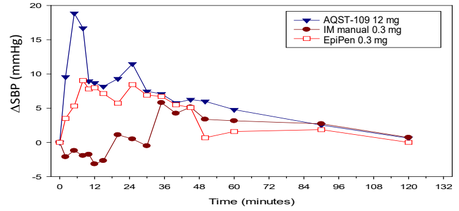


Figure 3: Mean Change from Baseline in Diastolic Blood Pressure

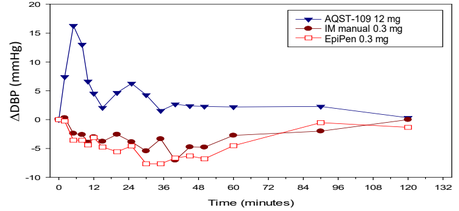
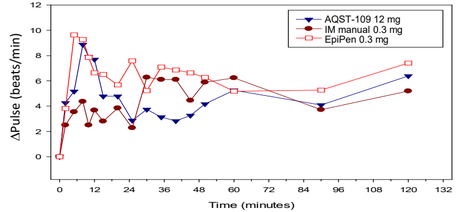


Figure 4: Mean Change from Baseline in Pulse



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

- **AQST-109 provides a distinct PK/PD profile relative to IM manual injection and EpiPen, with early PK and desired hemodynamic effects that are surrogate markers of the therapeutic effectiveness of epinephrine.**
- **Rapid absorption following sublingual administration produced the fastest observed median T_{max} (12 min for AQST-109, 23 min for EpiPen, and 45 min for IM injection).**
- **AQST-109 shows promise as a viable, noninvasive, easy-to-carry alternative for the treatment of anaphylaxis.**

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.
3. Mell HK, Mumma SN, Hiestand B, et al. *JAMA Surg.* 2017;152(10):983-984.

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. Greenhawt, Oppenheimer, Golden, Carmargo, Fleischer, Bernstein, and Lieberman, are members of the advisory board and consultants to Aquestive Therapeutics, Inc. Dr. Freedman is an employee of Pharma Medica Research, Inc. Drs. Slatko and Wargacki are employees of Aquestive Therapeutics.