PHARMACOKINETICS AND PHARMACODYNAMICS OF EPINEPHRINE FOLLOWING ADMINISTRATION VIA SUBLINGUAL FILM, AUTO-INJECTOR, OR MANUAL INJECTION

034

David Golden MD[1], Jay Lieberman MD[2], David Bernstein MD[3], John Oppenheimer MD[4], Mark L. Freedman MD[5], Carl Kraus MD[6], Steve Wargacki PhD[6]

[1]Medstar Franklin Square Hospital, Baltimore, MD , [2]University of Tennessee Health Science Center, Memphis, TN, [3]University of Cincinnati College of Medicine, [4]UMDNJ Rutgers University School of Medicine, [5]Pharma Medica Research Inc., [6]Aquestive Therapeutics

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 until emergency services can arrive.
- AQST-109 (also called 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) and can be quickly administered by placing the film under the tongue and allowing it to dissolve in the saliva.

OBJECTIVES

- To compare the pharmacokinetics (PK) and pharmacodynamics (PD) of epinephrine following administration of AQST-109, epinephrine IM injection, and epinephrine auto-injectors (EAIs) in healthy adult subjects.
- To compare the safety and tolerability of epinephrine following administration of AQST-109, epinephrine IM injection, and EAIs in healthy adult subjects.

METHODS

STUDY DESIGN

- Data were pooled across two clinical studies in which healthy volunteers received either investigational product (AQST-109) or approved epinephrine injection products (all participants met the same inclusion/exclusion criteria).
- Both studies were randomized, open-label crossover trials evaluating PK and PD parameters for at least 240 minutes post-dose.
- During the studies, subjects received:
  - AQST-109 12 mg
  - Epinephrine 0.3 mg via EpiPen
  - Epinephrine 0.3 mg via Auvi-Q
  - Epinephrine 0.3 mg via IM injection

METHODS (cont'd)

KEY INCLUSION CRITERIA

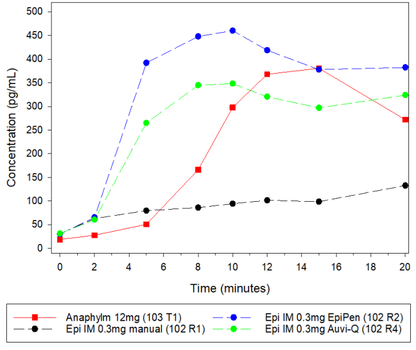
- Healthy adult males and females aged 18 to 50 years with a body mass index (BMI) between 18 and 30 kg/m^2.
- Systolic blood pressure (SBP) 95 to 140 mmHg, diastolic blood pressure (DBP) 55 to 90 mmHg, oxygen saturation ≥95% O_2, and pulse 50 to 100 beats/min.

RESULTS

PK DATA

- Delivery of AQST-109 resulted in epinephrine PK comparable to EAIs or IM (**Figure 1**).
- The partial area under the curve (AUC) values for AQST-109 were bracketed by the EAI and IM values for all timepoints between 8 and 60 minutes post-dose (**Table 1**).
- Median T_{max} for AQST-109 was similar to EpiPen and significantly faster than both Auvi-Q and IM (**Table 1**).

Figure 1: Geometric Mean Epinephrine Concentration over Time by Treatment (20 minutes)



RESULTS (cont'd)

Table 1: Epinephrine PK Parameters by Treatment

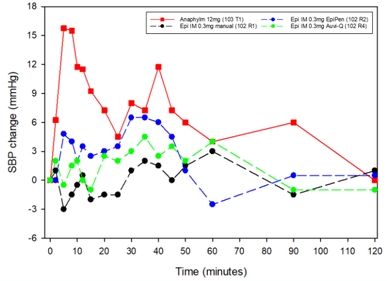
Parameter[a]	AQST-109 (n=22)	EpiPen (n=26)	Auvi-Q (n=28)	IM Manual (n=26)
T_{max}, min	15	10	30	50
C_{max}, pg/mL	457 (120.28)	628 (47.82)	646 (48.66)	344 (59.93)
AUC_{0-10}, h·pg/mL	13.9	43.5	26.5	5.3
AUC_{0-20}, h·pg/mL	66.1	105.7	72.0	16.1
AUC_{0-30}, h·pg/mL	96.4	176.6	136.8	38.0
AUC_{0-45}, h·pg/mL	127.6	267.2	249.7	94.4

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

PD DATA

- An early and rapid increase was observed in SBP (**Figure 2**), DBP (**Figure 3**), and pulse (**Figure 4**) with AQST-109 compared to the EAIs or IM.
- In the first 10-15 minutes after administration, SBP and DBP responses were most pronounced with AQST-109 (**Figure 2** and **Figure 3**).
- AQST-109 induced a similar overall PD response across all parameters (SBP, DBP, and pulse) when compared to the EAIs or IM.

Figure 2: Median Change from Baseline in Systolic Blood Pressure



RESULTS (cont'd)

Figure 3: Median Change from Baseline in Diastolic Blood Pressure

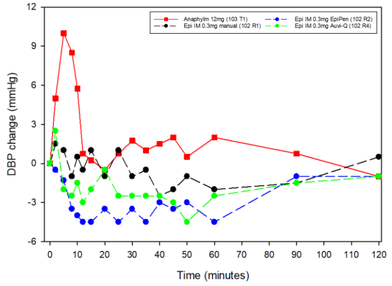
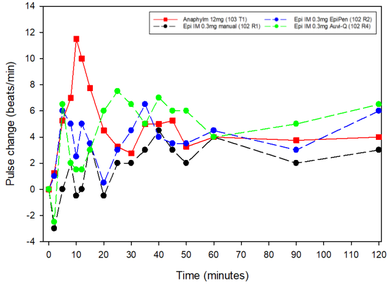


Figure 4: Median Change from Baseline in Pulse



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 in both studies.
- All reported TEAEs were mild, transient, or resolved with minimal intervention.

CONCLUSIONS

- **The AQST-109 formulation delivered epinephrine within range of the approved EAIs (EpiPen and Auvi-Q) and IM manual injection based on the PK profile.**
- **The rapid pronounced PD response from AQST-109 may be clinically meaningful to alleviate symptoms of anaphylaxis.**
- **Similar to all prior studies to date, AQST-109 is safe and well tolerated at the therapeutic dose.**
- **AQST-109 shows promise as a viable, noninvasive, needle-free, easy-to-carry alternative for the treatment of type 1 allergic reactions, including 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.

ACKNOWLEDGMENTS

This study was sponsored by Aquestive Therapeutics.

DISCLOSURES

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