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Integrated phase I pharmacokinetics and pharmacodynamics of epinephrine administered through sublingual film, autoinjector, or manual injection

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ABSTRACT

Background: Epinephrine is the first-line treatment for anaphylaxis and is administered through intramuscular or subcutaneous injection. AQST-109, a sublingual film containing the prodrug epinephrine, was developed as an alternative delivery method for treating severe allergic reactions, including anaphylaxis.
Objective: To compare the pharmacokinetics (PK) and pharmacodynamics (PD) of epinephrine after the administration of AQST-109 with those of epinephrine delivered by manual intramuscular injection and epinephrine autoinjectors.
Methods: Data were integrated from 2 randomized, open-label, phase I crossover trials that evaluated the PK and PD of epinephrine in 54 healthy volunteers. They had no previous medical conditions and were delivered either AQST-109 12 mg or 0.3 mg EpiPen, 0.3 mg generic EpiPen, 0.3 mg Auvi-Q, and 0.3 mg manual intramuscular injection.
Results: AQST-109 yielded comparable epinephrine PK and exposure to both manual intramuscular injections and epinephrine autoinjectors. The median time to maximum concentration (Tmax) for AQST-109 was 15 minutes, compared with EpiPen (10 minutes), generic EpiPen (15 minutes), Auvi-Q (30 minutes), and manual intramuscular injection (50 minutes). There was also an early, rapid, and consistent increase in systolic blood pressure, diastolic blood pressure, and heart rate after the administration of AQST-109.
Conclusion: AQST-109 delivered epinephrine with PK and PD results within the bracketed range of approved intramuscular products. AQST-109 has promise as an innovative, needle-free, nondevice, portable, and orally delivered alternative for first-line treatment of type I allergic reactions, including anaphylaxis.

Introduction

Epinephrine is the first-line treatment for anaphylaxis and is approved by the US Food and Drug Administration (FDA) for administration through the intramuscular and subcutaneous routes.[1-3] In August 2024, the FDA also approved a new nasal spray formulation based on comparisons with the established "gold standard" injection products, as currently required for any new epinephrine product.[4]

Traditional epinephrine autoinjectors (EAIs) present several challenges for timely and effective treatment during acute allergic reactions, including low device carriage rates, delayed administration or non-use mainly due to needle phobia, and erroneous use of EAIs.[3,5-7] When advised to carry 2 doses at all times, less than 50% of patients carry their EAI devices often due to device size and perceived inconvenience.[6] When considering those who do carry their EAI, 30% of patients and caregivers fail to administer the medication promptly and correctly.[8-10] Such barriers underscore a significant unmet need for a more convenient and less invasive delivery method.

Further barriers to epinephrine use include difficulties in patient and caregiver recognition of when to treat anaphylaxis and limited access to medication devices due to cost or supply chain issues.[11] These challenges complicate the timely and effective management of anaphylactic reactions. Ultimately, these obstacles contribute to delays or failures in the administration of epinephrine at the onset of anaphylaxis, which is associated with more severe reactions, persistent anaphylaxis, biphasic reactions, hospitalization, and intensive care unit admissions.[12-14]

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Sublingual drug delivery offers the potential to achieve therapeutically appropriate drug kinetics for compounds that can readily traverse the short mucosal barrier and rapidly become functionally active.[15] This method is particularly advantageous for epinephrine delivery, using the rich vascular network within 100 μm of the mucosal surface to ensure rapid absorption and systemic distribution. Because epinephrine typically induces vasoconstriction, using an epinephrine prodrug is beneficial in mitigating the reduced blood flow often associated with standard epinephrine administration.[16] Prodrugs can quickly convert into their active form, facilitating fast and complete systemic absorption. Furthermore, prodrugs can be engineered to enhance chemical stability, solubility, and permeability of the final drug product.[17]

AQST-109 is a sublingual film that delivers a novel prodrug of epinephrine under development for the emergency treatment of type I allergic reactions, including anaphylaxis. AQST-109 is the first and only orally delivered nondevice epinephrine product candidate currently in development and, if approved, would provide an alternative to current treatment options. This study aimed to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of epinephrine after the administration of AQST-109 in comparison with manual epinephrine intramuscular injection and EAIs, which are the current standards of care.

Methods

Study Design and Population

A pooled analysis was conducted by aggregating data from 2 randomized, open-label, crossover phase 1 clinical trials. These trials compared the PK and PD of epinephrine from 12 mg sublingual film (AQST-109, Aquestive Therapeutics, Inc., Warren, NJ) with manual intramuscular injection of epinephrine 0.3 mg (Belcher Pharmaceuticals, LLC, Largo, FL) and multiple EAIs inclusive of 0.3 mg EpiPen (Viatris, Canonsberg, PA), 0.3 mg generic equivalent to EpiPen (Teva Pharmaceuticals, Parsipanny, NJ), and 0.3 mg Auvi-Q (Kaleo, Inc, Richmond, VA). The studies used identical inclusion and exclusion criteria, including the following key criteria: healthy adult males and females aged 18 to 50 years, body mass index from 18 to 30 kg/m^2, systolic blood pressure (SBP) between 95 and 140 mm Hg, diastolic blood pressure (DBP) between 55 and 90 mm Hg, oxygen saturation of more than or equal to 95% O_2, heart rate (HR) between 50 and 100 beats per minute (bpm), and not having any previous medical condition such as any severe allergic reactions or cardiovascular disease, including hypertension, that in the opinion of the investigator would jeopardize the safety of the subject or affect the validity of the study results.

The 2 study protocols were approved by Optimum Clinical Research Inc Ethics Review Board and were conducted in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice. Before their involvement in the clinical study, all participants provided written informed consent and were compensated for their involvement. The studies were in phase I and did not require trial registration.

Pharmacokinetic and Pharmacodynamic Analysis

Subjects from the 2 phase I studies (n = 54) were administered either the investigational drug product (AQST-109) or one of the reference drug products (manual intramuscular injection, EpiPen, EpiPen generic, and Auvi-Q). The primary objective of this study was to compare the PK of baseline-corrected epinephrine after single doses of AQST-109 with that after the administration of each reference epinephrine drug product in healthy adult subjects with respect to the maximum observed plasma concentration (C_{max}) and drug exposure at specific time points (area under the curve [AUC]). The participants were randomly assigned to 1 treatment sequence according to a predetermined computer-generated randomization scheme. There was a 2-week washout period between film administration, and all doses were administered at the same time each day. Blood samples were collected at identical time points: before dosing (predose) and up to at least 240 minutes after dosing (postdose). To focus on the critical treatment window for anaphylaxis, the results are presented for time points up to 60 minutes. Although the therapeutic serum level of epinephrine has not been established, 100 pg/mL was used as a known threshold for PD activity[18] and being a focus of interest by the US FDA (2023 Pulmonary-Allergy Drugs Advisory Committee, PADAC). The proportion of subjects reaching 100 pg/mL within 5, 10, 15, 20, 30, 45, and 60 minutes postdose was assessed; however, only the 10- and 15-minute postdose data were presented in the PK results. PD analysis assessed hemodynamic measures, including SBP, DBP, and HR, all of which were baseline corrected by subtracting the average of the last 2 predose measurements from each respective time point.

Acknowledging the differences between approved epinephrine products and the variability of individual products, the FDA adopted a pragmatic approach to assess biocomparability through “PK bracketing.” New epinephrine formulations should have PK characteristics between those of the EAI products and manual epinephrine injections (2023 PADAC). The PK profiles of EpiPen, generic EpiPen, Auvi-Q, and manual intramuscular injections were used to establish the range of PK variability against which AQST-109 was compared. Standard PK parameters, including C_{max}, AUC, and T_{max}, were determined. The time taken to reach a target plasma epinephrine concentration of 100 pg/mL postdose was considered as an indicator of the time to physiological effects.

Statistical Analysis

In both studies, descriptive statistics were presented for baseline-corrected and -uncorrected epinephrine plasma concentrations, PK parameters, and PD parameters (SBP, DBP, and HR) at each nominal time point for each treatment. When statistical comparisons were made, analysis of variance was conducted using GraphPad Prism (version 10.3.1 for Windows, GraphPad Software, Boston, MA) to determine whether there were statistically significant differences between treatments. After analysis of variance, appropriate post hoc analyses were performed to identify specific group differences.

Results

Study Populations

Data from 134 exposures across 54 participants were pooled. The baseline demographic data of the subjects are found in Table 1. There were 22 patients who received AQST-109, 27 who received manual intramuscular injections, 27 who received EpiPen, 29 who received generic EpiPen, and 29 who received Auvi-Q. All dosed subjects were included in the PK and PD data sets.

Pharmacokinetics

The administration of AQST-109 yielded comparable epinephrine PK and similar exposure to both manual intramuscular injection and EAIs (Table 2, Fig. 1). The geometric mean peak concentration (C_{max}) was 497.9 pg/mL (95% CI 314.8-787.4) after AQST-109 administration. This was within the range observed for the comparators which were 391.0 pg/mL (95% CI 317.7-481.2) after manual intramuscular injection, 669.9 pg/mL (95% CI 541.5-828.7) after EpiPen administration, 620.7 pg/mL (95% CI 476.5-808.5) after EpiPen generic administration, and 688.4 pg/mL (95% CI 560.4-845.6) after Auvi-Q administration. The exposure (partial AUC) values for AQST-109 at all time points between 10- and 60-minute postdose were bracketed

Table 1
Baseline Demographics

Demographic characteristic	Drug product				
	AQST-109 12 mg N = 22	Manual intramuscular 0.3 mg N = 27	EpiPen 0.3 mg N = 27	EpiPen generic 0.3 mg N = 29	AUVI-Q 0.3 mg N = 29
Sex, n (%)					
Female	10 (45.5)	10 (37.0)	10 (37.0)	10 (34.5)	10 (34.5)
Male	12 (54.5)	17 (63.0)	17 (63.0)	19 (65.5)	19 (65.5)
Age (y)					
Mean (95% CI)	38 (34-42)	38 (34-41)	38 (34-41)	37 (34-41)	37 (34-41)
Weight (kg)					
Mean (95% CI)	73.2 (68.1-78.4)	73.9 (69.5-78.4)	73.9 (69.5-78.4)	74.5 (70.2-78.8)	74.5 (70.2-78.8)
Height (cm)					
Mean (95% CI)	168.4 (164.5-172.2)	169.0 (165.8-172.2)	169.0 (165.8-172.2)	169.8 (166.5-173.0)	169.8 (166.5-173.0)
BMI (kg/m^2)					
Mean (95% CI)	25.8 (24.7-26.8)	25.7 (24.7-26.8)	25.7 (24.7-26.8)	25.7 (24.7-26.7)	25.7 (24.7-26.7)

Abbreviations: BMI, body mass index; N, number of subjects included in each data set; n, number of subjects in each category; %, proportion of subjects in each category.
NOTE. This table includes data for the subjects included in the pharmacokinetic and pharmacodynamic data sets.

using manual intramuscular injection and EAIs (Table 2). Notably, the critical early time points within the first 30 minutes of AQST-109 administration exhibited exposure levels similar to those observed for EAIs.

AQST-109 demonstrated rapid and consistent PK outcomes, achieving C_{max} within 15 minutes of administration, indicating rapid epinephrine exposure (Fig. 1A and B). The median (IQR) time to maximum concentration (T_{max}) for AQST-109 was 15.0 (10.0-20.0) minutes (Table 2). In contrast, Auvi-Q and manual intramuscular injections exhibited higher T_{max} values than AQST-109, EpiPen, and generic EpiPen. Specifically, the median (IQR) T_{max} was 50.0 (45.0-50.0) minutes after manual intramuscular injection, 10.0 (5.0-25.0) minutes after EpiPen administration, 15.0 (5.0-35.0) minutes after EpiPen generic administration, and 30.0 (8.0-35.0) minutes after Auvi-Q administration. Significant differences in T_{max} values were observed between manual intramuscular injection and AQST-109 ($P < .05$). Similarly, the EpiPen, generic EpiPen, and Auvi-Q groups demonstrated a significant difference relative to the manual intramuscular group ($P < .05$).

There were 18 subjects (81.8%) who achieved a plasma epinephrine concentration of 100 pg/mL within 10 minutes of AQST-109 administration, whereas 20 (90.9%) reached this threshold within 15 minutes of AQST-109 administration. After manual intramuscular injection, only 15 patients (55.6%) achieved a plasma epinephrine concentration of 100 pg/mL within 10 minutes, whereas 16 patients (59.3%) reached this threshold in 15 minutes after administration. All 27 patients (100.0%) reached a plasma epinephrine concentration of 100 pg/mL within 10- and 15-minute post-administration after EpiPen administration. For generic EpiPen, 26 subjects (89.7%) achieved a plasma epinephrine concentration of 100 pg/mL within 10 and 15 minutes after administration. After Auvi-Q administration, 26 patients (89.7%) achieved a plasma epinephrine concentration of 100 pg/mL within 10 minutes, whereas 27 patients (93.1%) reached 100 pg/mL 15 minutes after administration.

Pharmacodynamics

The median changes in SBP, DBP, and HR from baseline are found in Figure 2A-C respectively.

The median (IQR) SBP peak effect (E_{max}) was 26.3 (18.0-34.0) mm Hg after AQST-109 administration, significantly greater in value (but overlapping in range) to the median (IQR) SBP E_{max} after manual intramuscular injection (10.0 [−11.0 to 13.0] mm Hg), EpiPen (13.5 [−11.0 to 18.5] mm Hg), EpiPen generic (10.5 [−12.5 to 17.5] mm Hg), and Auvi-Q (11.0 [−11.5 to 23.3] mm Hg) administration ($P < .05$ for AQST-109 vs each intramuscular method). The median (IQR) DBP E_{max} was 12.5 (9.3-16.6) mm Hg after AQST-109 administration, significantly exceeding the value (but overlapping in range) of the DBP median [IQR] E_{max} after manual intramuscular injection (−4.5 [−8.0 to 9.5] mm Hg), EpiPen (−9.5 [−15.5 to −3.0] mm Hg), EpiPen generic (−6.5 [−10.0 to 8.3] mm Hg), and Auvi-Q (−6.0 [−12.8 to 8.0] mm Hg) administration ($P < .05$ for AQST-109 vs each intramuscular method). The median (IQR) HR E_{max} was 16.8 (11.6-27.5) bpm after AQST-109 administration, which was higher than the median [IQR] HR E_{max} after manual intramuscular injection (12.0 [−7.5 to 19.0] bpm), Epi-

Table 2
Integrated Pharmacokinetic Parameters

Drug product	N	C_{max} (pg/mL) Geometric mean (95% CI)	AUC_{0-10} (h*pg/mL) Geometric mean (95% CI)	AUC_{0-20} (h*pg/mL) Geometric mean (95% CI)	AUC_{0-30} (h*pg/mL) Geometric mean (95% CI)	AUC_{0-45} (h*pg/mL) Geometric mean (95% CI)	AUC_{0-60} (h*pg/mL) Geometric mean (95% CI)	Median T_{max} (min) (IQR)
AQST-109 12 mg	22	497.9 (314.8-787.4)	17.9 (11.4-28.1)	79.2 (49.9-125.6)	115.1 (74.0-179.0)	153.5 (101.5-229.9)	189.4 (131.4-273.0)	15.0 (10.0-20)
Manual intramuscular injection 0.3 mg	27	391.0 (317.7-481.2)	12.9 (10.1-16.5)	31.3 (25.2-39.1)	59.8 (49.3-72.5)	128.1 (105.5-155.4)	206.1 (170.8-248.6)	50.0 (45.0-50.0)
EpiPen 0.3 mg	27	669.9 (541.5-828.7)	51.2 (39.6-66.3)	120.4 (94.7-153.0)	197.5 (158.7-245.9)	297.1 (244.7-360.8)	368.0 (308.6-438.8)	10.0 (5.0-25.0)
EpiPen generic 0.3 mg	29	620.7 (476.5-808.5)	47.7 (33.0-69.0)	102.3 (74.0-141.5)	165.0 (122.5-222.2)	257.9 (198.3-335.4)	327.6 (258.3-415.6)	15.0 (5.0-35.0)
AUVI-Q 0.3 mg	29	688.4 (560.4-845.6)	38.7 (26.7-55.9)	94.2 (67.2-132.1)	164.7 (122.7-221.1)	284.5 (222.5-363.7)	367.1 (294.1-458.3)	30.0 (8.0-35.0)

Abbreviations: AUC, area under the curve; Cmax, maximum plasma concentration over the sampling period; N, number of subjects; Tmax, time of the maximum plasma concentration over the sampling period.
NOTE. 95% CI of geometric mean is reported.

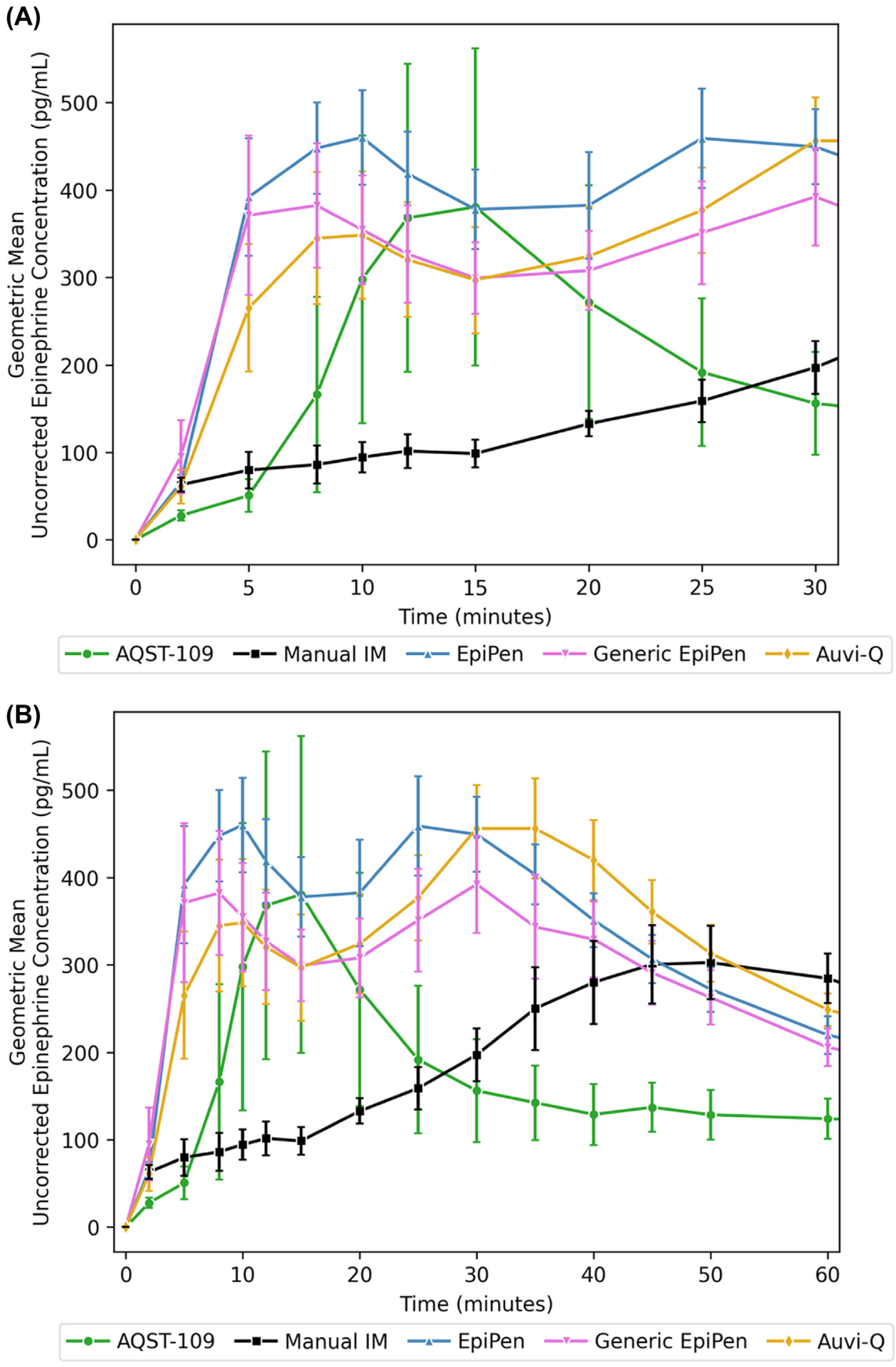

Figure 1. Geometric mean (±SE) uncorrected epinephrine concentration up to (A) 30 minutes post-administration and (B) 60 minutes post-administration. IM, intramuscular.

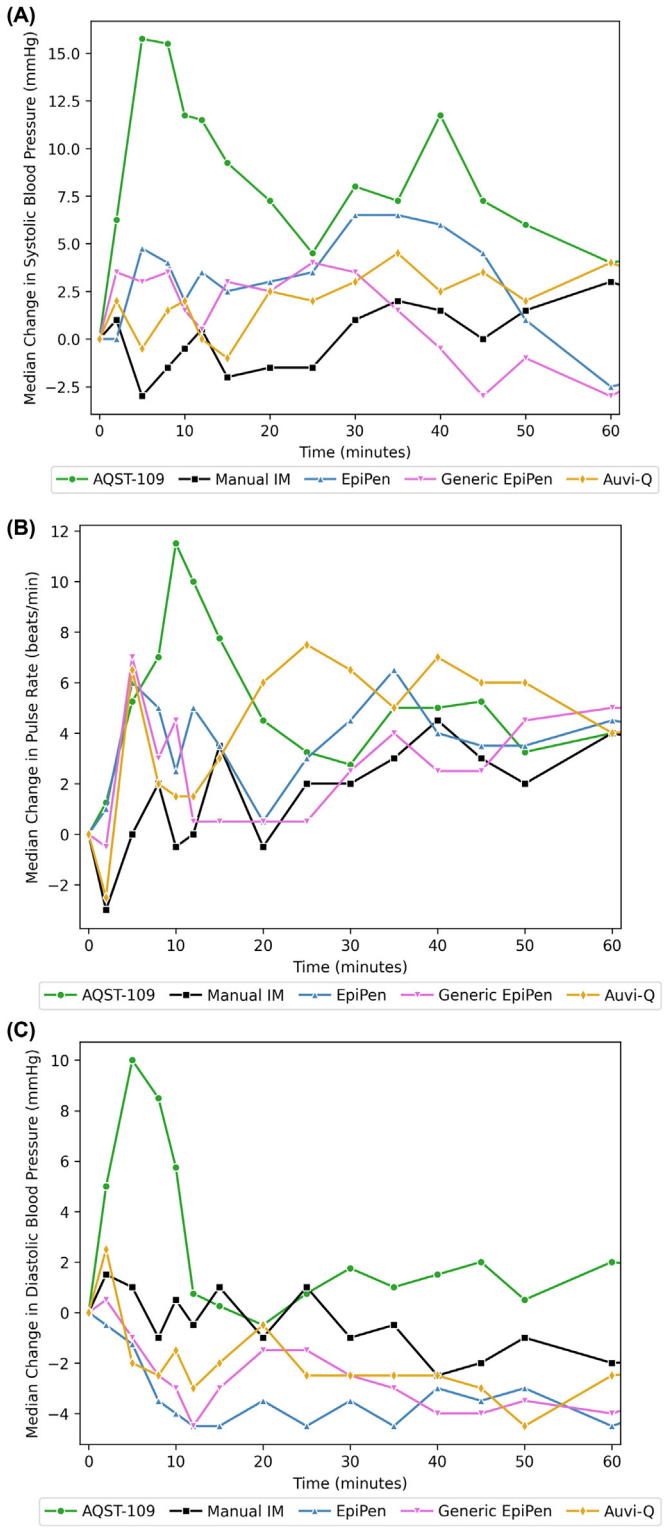

Figure 2. Median change from baseline up to 60 minutes in (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate. IM, intramuscular.

Pen (14.0 [10.0-19.5] bpm), and EpiPen generic (13.5 [9.0-21.3] bpm) administration and was comparable to the median (IQR) HR E_{max} after Auvi-Q (17.5 [12.3-22.3] bpm) administration; however, significant differences were not observed.

The median time to maximum effect (TE_{max}) for SBP was 9.0 minutes after AQST-109 administration, which was shorter than the median SBP TE_{max} after manual intramuscular injection (34.0 minutes), EpiPen (29.0 minutes), EpiPen generic (29.0 minutes), and Auvi-Q (29.0 minutes) administration (Table 3); however, significant differences were not observed. The median DBP TE_{max} was 7.0 minutes after AQST-109 administration, which was shorter than the median DBP TE_{max} after manual intramuscular injection (39.0 minutes; P = .01), EpiPen (29.0 minutes; P = 0.04), EpiPen generic (34.0 minutes; P = 0.005), and Auvi-Q (24.0 minutes; not significantly different) administration. The median HR TE_{max} was 11.0 minutes after AQST-109 administration, which was shorter than the median HR TE_{max} after manual intramuscular injection (39.0 minutes), EpiPen (19.0 minutes), and Auvi-Q (29.0 minutes) administration, but slightly longer than the median HR TE_{max} after EpiPen generic (9.0 minutes) administration, without significant differences observed.

Overall, across all 3 PD parameters, AQST-109 had an earlier and more rapid increase than both EAIs and manual intramuscular injections. In addition, all PD changes remained within the physiological range and were similar to that of EpiPen (Table 3). The SBP and DBP values observed with AQST-109 within the first 10 15 minutes of administration were more pronounced than those observed with EAIs and manual intramuscular injections.

Discussion

Overall, AQST-109 demonstrated rapid delivery of epinephrine into the bloodstream while achieving the FDA bracketing requirements compared with currently approved products. As an acute anaphylactic treatment, epinephrine is intended for early use to halt the progression of anaphylaxis and reverse multiorgan pathophysiological effects. Its administration should lead to the complete resolution of most anaphylactic reactions. In cases that require additional medical attention or supervision, epinephrine serves as a therapeutic bridge to emergency care. In the United States, 95% of 911 calls should be addressed within 10 minutes in urban areas and within 30 minutes in rural areas.[19] AQST-109 demonstrated similar or greater exposure levels to the EAIs and manual intramuscular injection within the first 10 minutes after dosing, indicating comparable exposure levels at critical early time points. In addition, key AQST-109 PK parameters reveal that AQST-109 consistently provided fast median T_{max} and mean C_{max} levels that aligned with or exceeded the current standards of care. Furthermore, AQST-109 achieved plasma concentrations of 100 pg/mL in 82.82% of subjects within 10 minutes and 90.91% of subjects within 15 minutes, similar to the EpiPen. This is particularly advantageous given the value of surpassing this therapeutic threshold as quickly as possible for rapid and effective physiological activity.[18]

Hypotension and syncope are common elements of anaphylactic reactions.[20,21] A therapeutic intervention that not only rapidly stabilizes mast cells but also provides rapid hemodynamic stability would be clinically advantageous. The response to AQST-109 administration revealed an earlier, more rapid, and consistent increase in SBP, DBP, and HR relative to the autoinjectors. In comparison to manual intramuscular injection and EAIs, SBP and DBP had a more pronounced response within 10 to 15 minutes of AQST-109 administration, even though the PK profile demonstrated a slower relative absorption, implying some distinct adrenergic activity related to the route of administration. These data suggest that the PK profile of AQST-109 would satisfy the bracketing requirements involving currently approved EAI products and that the PD profile of AQST-109 would be clinically supportive of patients with anaphylaxis.

Current standards of epinephrine drug delivery through intramuscular and subcutaneous injection result in a bimodal PK distribution, characterized by 2 peaks in the drug concentration-time profile.[22] This variability in the PK effect of parenterally administered doses of epinephrine is driven by local vasoconstriction at the site of

Table 3
Integrated Pharmacodynamic Parameters

Drug product	N	E_{max} Median (IQR)			TE_{max} Median (IQR)		
		SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)
AQST-109 12 mg	22	26.3 (18.0-34.0)	12.5 (9.3-16.6)	16.8 (11.6-27.5)	9.0 (4.0-40.3)	7.0 (4.0-15.3)	11.0 (7.0-190.0)
Manual intramuscular injection 0.3 mg	27	10.0 (−11.0 to 13.0)	−4.5 (−8.0 to 9.5)	12.0 (−7.5 to 19.0)	34.0 (14.0-59.0)	39.0 (19.0-89.0)	39.0 (14.0-119.0)
EpiPen 0.3 mg	27	13.5 (−11.0 to 18.5)	−9.5 (−15.5 to −3.0)	14.0 (10.0-19.5)	29.0 (7.0-59.0)	29.0 (7.0-59.0)	19.0 (4.0-44.0)
EpiPen generic 0.3 mg	29	10.5 (−12.5 to 17.5)	−6.5 (−10.0 to 8.3)	13.5 (9.0-21.3)	29.0 (6.5-59.0)	34.0 (17.5-89.0)	9.0 (4.0-46.5)
AUVI-Q 0.3 mg	29	11.0 (−11.5 to 23.3)	−6.0 (−12.8 to 8.0)	17.5 (12.3-22.3)	29.0 (10.0-34.0)	24.0 (6.5-89.0)	29.0 (9.0-39.0)

Abbreviations: BPM, beats per minute; DBP, diastolic blood pressure; Emax, maximum change from baseline within 60 minutes; HR, heart rate; N, number of subjects; SBP, systolic blood pressure; TEmax, time to achieve maximum change from baseline within 60 min.

injection. All other confounding influences that resulted in the bimodal peak were associated with the location of administration and differences in the amount of epinephrine that was initially absorbed vs the amount of epinephrine that was absorbed once vasoconstriction subsided. This variability creates complexity when a second dose of epinephrine is clinically necessary after 5 to 10 minutes, even though the maximum plasma concentrations from the first dose may be delayed by 30 to 45 minutes after administration.[23] The prodrug design in AQST-109 limits vasoconstriction, thereby eliminating the bimodal PK distribution and resulting in uniform and predictable plasma concentrations with consistency in timing, potentially allowing patients and caregivers to more accurately determine the need and timing for repeat dosing.

Sublingual administration may also circumvent unwanted PD effects, particularly the initial decrease in DBP associated with intramuscular injections. All intramuscular administration methods resulted in a decrease in DBP after administration (Fig. 2B), whereas AQST-109 exhibited a notably pronounced increase in DBP. The observed result may be due to sublingual administration of epinephrine avoiding the β2-mediated vasodilation resulting from direct injection into the skeletal muscle, effectively mitigating the drop in DBP observed after intramuscular administration. This may aid in maintaining overall blood pressure and reducing the risk of hypotension and subsequent shock in patients experiencing anaphylaxis. The same phenomenon of limiting the decrease in DBP was noted with the intranasal administration of epinephrine.[24]

In addition, sublingual epinephrine circumvents some of the most important barriers to epinephrine use, leading to improved outcomes. By providing a portable and less invasive delivery route, AQST-109 could facilitate easier administration and earlier use at the beginning of the reaction, potentially resulting in fewer severe or biphasic reactions, and fewer emergency department visits or hospitalizations. In addition, AQST-109 uses an epinephrine prodrug to optimize bioavailability and extend shelf life[17] while minimizing unwanted local effects associated with direct drug delivery.

This study had several limitations. First, consistent with any study involving epinephrine, it is ethically infeasible to assess PK, PD, and symptom responses in patients with severe allergic reactions. Consequently, the approval pathway for epinephrine products relies on demonstrating similarities in PK, PD, and safety data with established products within the FDA-approved bracketed ranges. This study was conducted in healthy adults who were not experiencing allergic reactions or any concurrent illnesses at the time of the study; factors that could potentially influence PK or PD responses to epinephrine, regardless of the delivery method. Second, although the sample size was small, it was appropriately powered by using healthy volunteers to test 2 different products (separated by FDA-approved washout periods) to ensure adequate statistical power. Third, although the FDA has provided bracketed ranges, there is currently no established therapeutic serum level for epinephrine and no validated correlation between T_{max} or C_{max} and clinical outcomes when treating anaphylaxis, which is a limitation that is not specific to this product.

This analysis revealed that the AQST-109 formulation delivered epinephrine with PK and PD profiles within the range of manual intramuscular injection and EAI currently on the market in the United States. This sublingual delivery formulation offers a novel alternative to injection-based epinephrine delivery, overcoming the well-known barriers associated with the current epinephrine administration methods. Overall, AQST-109 has promise as an innovative, needle-free, nondevice, portable, and orally delivered alternative for first-line treatment of type I allergic reactions, including anaphylaxis.

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Disclosures

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reports serving as consultant/advisor for ARS Pharmaceuticals, Bryn Pharma, and Aquestive Therapeutics.

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