(L37) A Phase 1, Randomized Study Evaluating the Safety Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Single Ascending Doses of Epinephrine Prodrug 109 Sublingual Film (AQST-109) in Healthy Male Volunteers

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INTRODUCTION

- Although epinephrine has been in use for more than a century, epinephrine auto injectors (EAI) are often under utilized due to various factors including needle phobia, delayed administration and failure to carry[1,2].
- Obstacles for patients and caregivers include incorrect use and lack of response. Incorrect use and delayed injection of epinephrine have been reported as primary reasons for lack of response in the treatment of anaphylaxis[3].
- Incorrect use of epinephrine injectors has also resulted in needle injuries. Lack of response to epinephrine has also been associated with the malfunction of the auto-injectors[4,5].
- Consequently, a different treatment modality could address significant unmet need resulting from deficiencies of auto-injectors and improve patient access, usage, and therapeutic response[5].
- To date, alternative delivery routes for epinephrine have failed to produce the speed and observed plasma levels (Cmax) produced by the Standard of Care (EpiPen).
- *Aquestive Therapeutics* is developing a sublingual (SL) film containing AQST-109 (a prodrug of Epinephrine) delivered using PharmFilm technology[6].
- The targeted indication for AQST-109 is the same as that for Epinephrine injection in the emergency treatment of Type 1 allergic reactions, including anaphylaxis.
- The target formulation and dose for AQST-109 is one that results in exposure that is comparable to that of commonly used epinephrine IM injections, such as 0.3 mg EpiPen®.
- This study demonstrates important safety and tolerability of AQST-109 and provides the PK/PD information of tested formulations that will define the eventual dose and the final formulation for a future bioequivalence study with epinephrine IM injection (such as EpiPen®).

OBJECTIVES

Primary objective:

- The primary objective of this study was to assess the safety and tolerability of AQST-109 across 4 film formulations ranging from 3 mg up to 24 mg, in healthy young male volunteers.

Secondary objectives:

- To assess the PK of AQST-109 and epinephrine following SL administration as a function of dose as well as across the 4 film formulations.
- To compare descriptively the PK and PD (Heart Rate, Systolic and Diastolic Blood Pressure) following SL administration of the 4 formulations of AQST-109.

METHODS

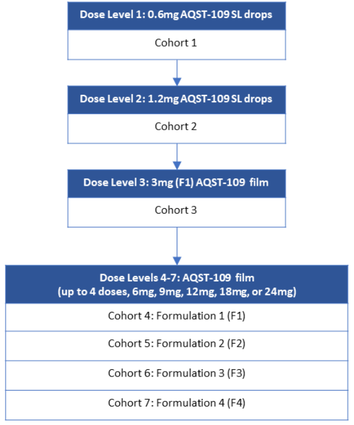
STUDY DESIGN

- This was a two-center, Phase 1, Open label, randomized, SAD, safety-tolerability, PK, and PD study of AQST-109 SL drops and 4 SL film formulations of AQST-109 in young healthy male volunteers under fasting conditions.

METHODS

- In two sequential cohorts (Cohorts 1 and 2), each consisting of 6 subjects, single ascending doses of 0.6 and 1.2 mg of AQST-109 drops are administered in a SL fashion. Subsequently, 6 additional subjects are assigned to receive a 3 mg film dose of AQST-109 (Cohort 3). Finally, 24 subjects are randomized into 1 of 4 cohorts (Cohorts 4 to 7), corresponding to 4 different film formulations of AQST-109.
- Cohort 4 receives the same formulation as the one used in Cohort 3: Formulation 1. Cohorts 5, 6, and 7 receive new formulations: Formulations 2, 3, and 4, respectively.
- Cohorts 4 to 7, each consisting of 6 subjects, initially receive the AQST-109 film at the 6 mg dose.
- A sample size of 6 subjects per dose level for each cohort is judged adequate to estimate AQST-109 and epinephrine PK parameters for selection of the next dose level and for assessment of safety and tolerability.
- The twenty-four subjects returned to receive single ascending SL doses up to 24 mg in a sequential fashion.
- Dose escalation stopping criteria were predefined as:
  - Two or more TEAE's determined to be moderate in severity or above
  - Average peak plasma concentrations exceeding 30% of the target level Cmax of 520 pg/mL, thus, values greater than 676 pg/mL would be considered as a stopping value

Figure 1: Study design



ANALYSIS

- Formulation 2 met the predefined stopping criteria after the 12mg dose. Formulation 1 met the stopping criteria after the 18 mg dose. Formulations 3 and 4 were escalated through 18mg but stopped without further escalation as study objectives were met.
- For this specific analysis, subjects that received either AQST-109 Formulation 1 (F1) or Formulation 2 (F2) at the 12 mg dosage strength were selected.
- Safety and tolerability data was reported using descriptive statistics.
- PK analysis was performed using Phoenix® WinNonlin®. Inferential statistical analyses was performed using SAS® according to FDA guidelines.
- Subjects were monitored for adverse events and local tolerability. PK and PD measurements (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) were taken pre-dose and frequently post-dose to 6 hours.
- EpiPen® data from a previous study was used as a historical comparator.

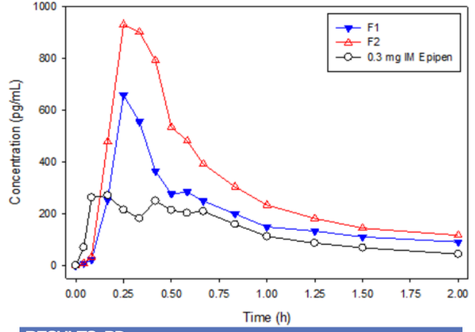
RESULTS - PK

- All formulations and dosage strengths evaluated in this study were well tolerated. No serious AE's were observed and local administration site AE's were mild and self-resolving.
- Dosing with F1 at 12mg resulted in a geometric mean Cmax and AUC0-t of 552 pg/mL and 634 hr*pg/ml, respectively (Table 1).
- Dosing with F2 at 12 mg resulted in a geometric mean Cmax and AUC0-t of 762 pg/mL and 603 hr*pg/ml, respectively (Table 1).
- The median Tmax for both formulations was 15 minutes.
- By comparison, EpiPen dosing resulted in a geometric mean Cmax and AUC0-t of 341 pg/mL and 328 hr*pg/ml, respectively.
- Figure 2 further illustrates the plasma concentration data over time following administration of the 2 formulations and 0.3 mg IM EpiPen, with F1 and F2 showing narrower span than Epipen.

Table 1: Baseline-Corrected Plasma Epinephrine PK After AQST-109 and 0.3mg IM EpiPen

PK Parameter	AQST-109 F1, 12mg (N=6)	AQST-109 F2, 12mg (N=8)	0.3mg IM EpiPen (N=10)
C_{max} (pg/mL)	552	762	341
Median T_{max} (minutes) (minimum, maximum)	15 (15-25)	15 (10-35)	22 (5-90)
AUC 0-t (hr*pg/mL)	634	603	328

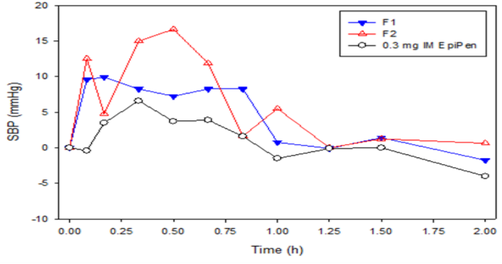
Figure 2: Mean Baseline-Corrected Plasma Epinephrine Concentration over Time Following Administration of AQST-109 and 0.3mg IM EpiPen



RESULTS- PD

- Figure 3 shows SBP changes over time following administration of F1, F2 and 0.3 mg IM EpiPen.
- AQST-109 shows a similar change from baseline systolic blood pressure when compared to EpiPen, with F2 presenting slightly larger variations over time.
- The data suggests a similar timing and magnitude of the hemodynamic effect from epinephrine without regard for the route of administration.

Figure 3: Mean Change from Baseline SBP over Time Following Administration of AQST-109 and 0.3mg IM EpiPen



CONCLUSION

- Dosing with AQST-109 resulted in Cmax and Tmax values comparable to published data for auto-injectors. Similarly, PD resulted in comparable changes to injected epinephrine,.
- AQST-109 SL film demonstrated consistent Tmax values in a tighter range than reported for injectable epinephrine.
- AQST-109 SL film formulations were safe and well-tolerated across all formulations and all dose levels.
- This is the first time it has been demonstrated that epinephrine could achieve therapeutic plasma concentrations following sublingual administration.
- AQST-109 sublingual film shows promise as a novel alternative for the treatment of anaphylaxis.

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DISCLOSURES

John Oppenheimer is a member of the Advisory board and has served as a consultant for Aquestive Therapeutics, Inc. Shawn Berg and Cathie Leister serve as a paid consultant to Aquestive Therapeutics, Inc. Steve Wargacki, Rajesh Kainthan, Ayman Kafal and Gary Slatko are employees of Aquestive Therapeutics, Inc.