Pharmacokinetics of a Novel Inhaled Epinephrine

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Are Current Treatments for Anaphylaxis Optimal?

No clinical trial efficacy data exists for current anaphylaxis treatments.

Non-clinical studies have demonstrated continuous epinephrine IV infusion returns MAP to baseline within 10 minutes.[1]
- More rapidly than IM or SC

Retrospective analysis of emergency room visits for anaphylaxis (n=142) demonstrated superiority of IV infusion over IM injection.[2]
- Faster symptom resolution (5 min vs 9 min)
- Lower overall dose (0.25 mg vs 0.3 mg)
- Lower Incidence of Adverse Events, fewer biphasic reactions

These data suggest that IV infusion is a superior treatment for anaphylaxis compared to IM or SC injection.

Simulating IV Infusion with an Inhaler

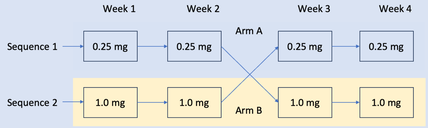
KP001 is a novel metered dose inhaler in development, designed to improve treatment of systemic allergic reactions, including anaphylaxis.
- Delivers drug to the lungs for rapid absorption into systemic circulation and more rapid attenuation of reaction
- Multiple inhalations can simulate the PK of continuous IV

KP001 is different than other epinephrine MDIs:

Reduced deposition in oral cavity optimizing delivery efficiency.
Improved delivery to upper airway (e.g., larynx) to reduce local edema.
Improved lung deposition to enhance systemic absorption and resolve systemic symptoms.
Less sensitivity to orientation of inhaler in mouth for improved ease of use.
More consistent performance across various flowrates to decrease inter-subject variability.

Study Design

First-in-human study to evaluate the safety and PK of 2 doses of inhaled epinephrine.
Study Type: Randomized, double-blind, placebo-controlled, crossover study.
Randomization: 3:1 active:placebo, sequence 1 or sequence 2.



Dosing

Low dose (0.25mg) is delivered as 2 inhalations of 0.125 mg spaced by ~15 seconds.

High dose (1.0mg) is delivered as 4 sets of 2 inhalations, where successive sets of inhalations are spaced by ~2 minutes.

Primary Objectives:

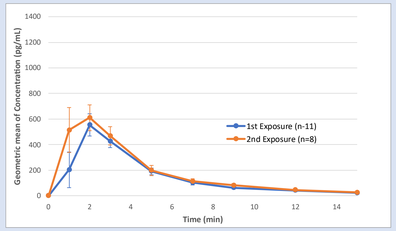
1. To evaluate the safety and tolerability of 2 different dose regimens of KP001in healthy adult volunteers.
2. To evaluate any carryover effect with a 7-day washout of 2 different dose regimens of KP001 in healthy adult volunteers.

Measurements

Pharmacokinetics: blood epinephrine concentrations measured pre-dose, and at 1, 2, 3, 5, 7, 9, 12, 15, 20, 30, 45, 60, 90 min, plus 2 & 6 hours post dose
Vital Signs: 2, 5, 10, 15, 20, 30, 40, 60 min, plus 2 & 6 hours post dose
Other: PFT, 12 lead ECG, pulse oximetry

Results

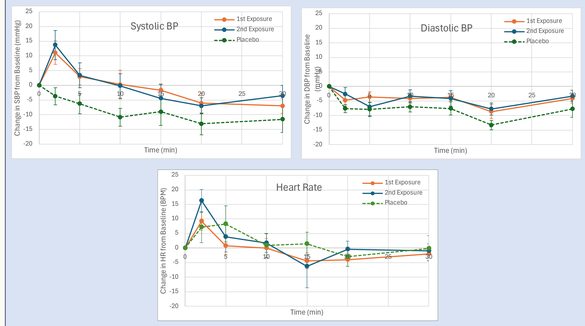
Pharmacokinetics of the low dose (0.25 mg)



	1st Exposure	2nd Exposure	Pooled
C_{max}	602 pg/mL	747 pg/mL	659 pg/mL
T_{max}	2.0 min	1.5 min	1.7 min
AUC_{0-3}	1050 pg*min/mL	1420 pg*min/mL	1190 pg*min/mL
AUC_{0-5}	1670 pg*min/mL	2110 pg*min/mL	1840 pg*min/mL
AUC_{0-t}	3250pg*min/mL	3330 pg*min/mL	3280 pg*min/mL

As expected for an inhaled small molecule, **absorption** is very fast with a T_{max} of ~2 minutes.
Elimination is consistent with the systemic half-life of about 3.4 minutes.
PK for the second exposure was higher, so the sufficiency of a 1-week washout period was not confirmed.
No physical depot of epinephrine to release drug over time.

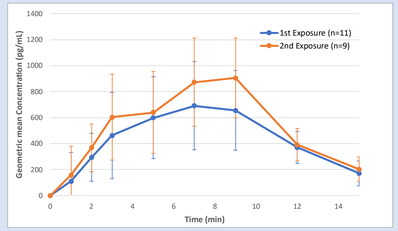
Pharmacodynamics of the low dose



1. Transient increase in **SBP** of 10-15 mmHg
   - Returned to baseline by 10 minutes
2. Minimal impact on **DBP**
3. Transient increase in **HR** of 10-15 bpm
   - Returned to baseline by 10 minutes

Results

Pharmacokinetics of the high dose (1.0 mg)

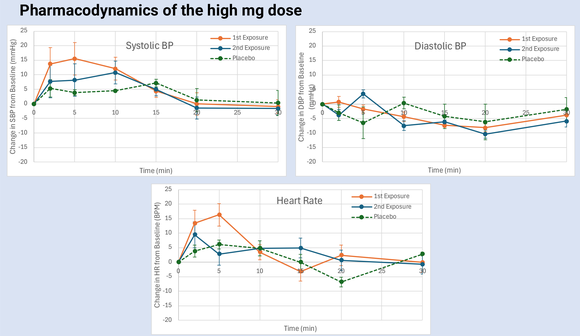


	1st Exposure	2nd Exposure	Pooled
C_{max}	899 pg/mL	1030 pg/mL	958 pg/mL
T_{max}	6.2 min	7.1 min	6.6 min
AUC_{0-3}	662pg*min/mL	867 pg*min/mL	748 pg*min/mL
AUC_{0-5}	1820pg*min/mL	2130 pg*min/mL	1950 pg*min/mL
AUC_{0-t}	9630 pg*min/mL	12007 pg*min/mL	10600 pg*min/mL

C_{max} does not scale linearly with dose.
- Increase from the second set of 2 inhalations will be offset by the rapid elimination from the first set (similarly for the 3rd and 4th set)

Once dosing has stopped, **elimination is slower** with a half-life of about 6.2 minutes.
PK for the second exposure was higher, so the sufficiency of a 1-week washout period was not confirmed.

Pharmacodynamics of the high mg dose



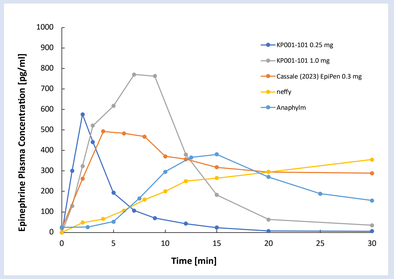
Transient increase in **SBP** of 10-15 mmHg
- Returned to baseline by 20 minutes

Minimal impact on **DBP**
Transient increase in **HR** of 10-15 bpm
- Returned to baseline by 20 minutes

Safety

The overall safety profile observed in the KP001-101 study was consistent with the expected pharmacologic effects of epinephrine and comparable to findings reported following administration of approved epinephrine auto-injectors.[3,4,5]

Comparison to other delivery routes



Epinephrine Delivery/Dose	C_{max}	T_{max} median (range)
KP001 2x125 µg (0.25 mg)	659 pg/mL	1.8 mins (1-2)
KP001 8x125 µg (1.0 mg)	958 pg/mL	6.6 mins (3-9)
EpiPen (Cassale) (0.3 mg)[6]	753 pg/mL	7.5 mins (2-45)
Neffy (2 mg)[7]	481 pg/mL	30 mins (6-150)
Anaphylm (12 mg)[8]	480 pg/mL	15 min (10-20)

Conclusions

1. KP001 was **safe and well tolerated.**

2. KP001 showed **rapid absorption** with a T_{max} of ~2min for the low dose.
   - *notably more rapid T_{max} and elimination compared to EpiPen and new needleless products*

3. **C_{max} did not scale with dose.**

4. The sufficiency of a 1-week washout period for crossover studies was not confirmed.

References:

1. Mink, S.N. et al. 2004. Clinical and Experimental Allergy 34 (11): 1776–83.
2. Fujizuka et al 2022 Acute Medicine & Surgery 9(1):e790.
3. Turner et al (2021) Clin & Exp Allergy. July: p. 1-11.
4. Lockey et al (2020) J Allergy Clin Immun: 145(2) p. AB78.
5. Dreborg & Kim (2021) Allergy, Asthma and Clin Immun 17(1): p 1-11).
6. Cassale et al (2023) J Allergy Clin Immun 152(6): 1587-1596.
7. FDA Briefing Document for Neffy, p11, May 23, 2023 .
8. Kraus et al. (2025) Ann Allergy Asthma Immunol 134(5): p. 580-586.

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