

Delivery of Epinephrine: Does the Route Matter?

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Learning Objectives

Be capable to explain a brief history of epinephrine

Explain how FDA process to approve new routes of administration of epinephrine

Analyze the data on PK and PD measurements in intranasal and sublingual epinephrine

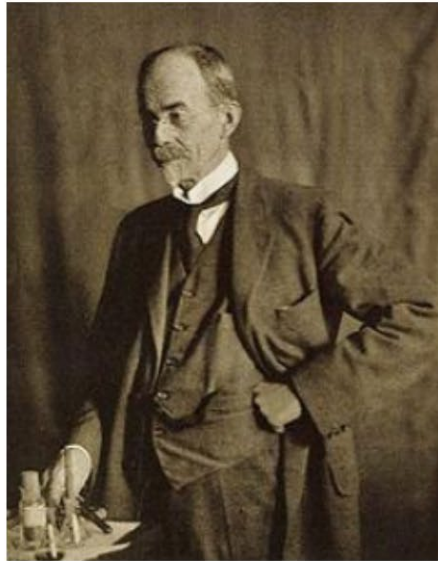
Conflicts of Interest

Sanofi, Regeneron, GSK, AstraZeneca, ALK, Bryn Pharma, Prollergy, Lanier Biotherapeutics, Hippo DX, and Nectar

A Brief History of Epinephrine

In 1893 by George Oliver, a Harrogate physician, and Edward Schäfer, professor of physiology at University College London made extract from adrenal glands contained a substance with dramatic pharmacological effects

However, a name for the substance was not coined until John Jacob Abel in the USA prepared crude adrenal extracts in 1897 and called them epinephrin [*sic*].



ON EPINEPHRIN, THE ACTIVE CONSTITUENT OF THE SUPRARENAL CAPSULE AND ITS COMPOUNDS.

By JOHN J. ABEL.

ACTING on Hyrtl's suggestion that *epinephris* would be the best name for the suprarenal capsule, the author has given the name Epinephrin to the active principle as isolated by him.

Aside from the chemical and physiological interest attaching to this substance it is believed that its careful study will throw light on the symptoms of Addison's disease.

When the benzoate of epinephrin is decomposed in the autoclave at pressures varying from 8 to 12 atmospheres, the resulting solution contains epinephrin; it no longer gives a rose-red color with iodine water and ammonia, but gives instead the fine emerald green which is always seen when ferric salts are added. All other reactions of epinephrin described in previous articles¹ are retained. The salts of epinephrin secured in this way possess but little physiological

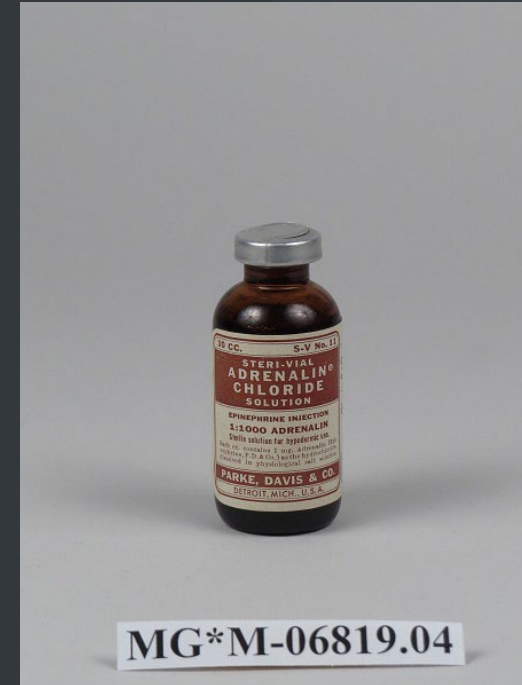
A Brief History of Epinephrine (cont.)

The first medical use of epinephrine occurred in 1901 by Solomon Solis-Cohen, who gave desiccated adrenal extract orally to treat patients with hay fever.

In 1901, Jokichi Takamine prepared a pure extract of the active principle from the adrenal gland and patented it.

Parke, Davis & Co marketed his extract and used the proprietary name Adrenalin. Epinephrine became the generic name in America.

In 1913, James Adam, author of *Asthma and its Radical Treatment*, noted that the “absorption of the drugs from the nasal mucous membrane or larynx or trachea” should be seen an alternative route for epinephrine.



A Brief History of Epinephrine (cont.)

The method of hypodermic administration of epinephrine was endorsed by a report from Dr. Brian Melland, published in *The Lancet* in 1920 and showed efficacy in asthma.

Bodon C. The intracardiac injection of adrenalin. *The Lancet* 1923; 1:586-590 popularized the use of epinephrine in anaphylaxis.

By the 1930s, epinephrine emerged as a frontline treatment for anaphylaxis due to its ability to rapidly reverse many of the symptoms associated with the condition.

Epinephrine/Adrenaline-Etymology

Greek: ἐπί (upon) + νεφρός (kidney)

Classical Latin: ad (placed on) + rēnēs (kidneys)

Greek “epinephrine” = Latin “adrenaline”

Which is Correct???

Is it Epinephrine or Adrenaline??

Is it Epinephrine or Adrenaline??

Most therapeutic medicines have at least three different names.

- The chemical name by the International Union of Pure and Applied Chemistry (IUPAC).
 - (R)1(3,4dihydroxyphenyl)2methylaminoethanol
- The approved (official or generic) name
 - World Health Organization's recommended international nonproprietary name (rINN)
- But it may be some locally approved name—
 - British approved name (BAN)
 - Dénomination commune française (DCF)
 - Japanese accepted name (JAN)
 - United States adopted name (USAN)
- (R)1(3,4dihydroxyphenyl)2methylaminoethanol is better known as adrenaline (BAN) or epinephrine (rINN).

Table 2 Pharmacopoeial names and the number (percentage) of times the names adrenaline and epinephrine have been used in bioscience titles or abstracts since 1965, by country of publication*

| Country of publication | Name in national pharmacopoeia or equivalent | Instances of “adrenalin(e)” | Instances of “epinephrin(e)” |
|---|--|-----------------------------|------------------------------|
| Australia | Adrenaline | 159 (85.0) | 28 (15.0) |
| United Kingdom (England, Northern Ireland, Scotland, Wales) | Adrenaline | 3573 (73.6) | 1 282 (26.4) |
| France | Adrenaline | 453 (69.3) | 201 (30.7) |
| Scandinavia (Denmark, Finland, Norway, Sweden) | Adrenaline† | 710 (68.5) | 327 (31.5) |
| Spain | Epinefrina | 75 (65.2) | 40 (34.8) |
| Italy | Adrenalina | 233 (59.4) | 159 (40.6) |
| Germany | Adrenalinum‡ | 1485 (58.3) | 1 062 (41.7) |
| Rest of the world | — | 3372 (55.4) | 2 214 (36.4) |
| Japan | Epinephrine | 441 (38.1) | 715 (61.9) |
| Canada | Epinephrine | 121 (28.7) | 301 (71.3) |
| United States | Epinephrine | 1157 (9.8) | 10 609 (90.1) |

*Papers (accessed on Medline) that used both adrenalin(e) and epinephrin(e) were excluded (they comprised under 1% of the total); the Medline records for 1965 are incomplete.

†No Nordic pharmacopoeia; Scandinavia follows the *European Pharmacopoeia*.

‡*Deutsches Arzneibuch*.

Is IM really best for anaphylaxis?

EpiPen approved by the FDA in 1987-inject into the anterolateral aspect of thigh
Simons et al. in 2001 published human study of IM vs SC

872 Simons, Gu, and Simons

J ALLERGY CLIN IMMUNOL
NOVEMBER 2001

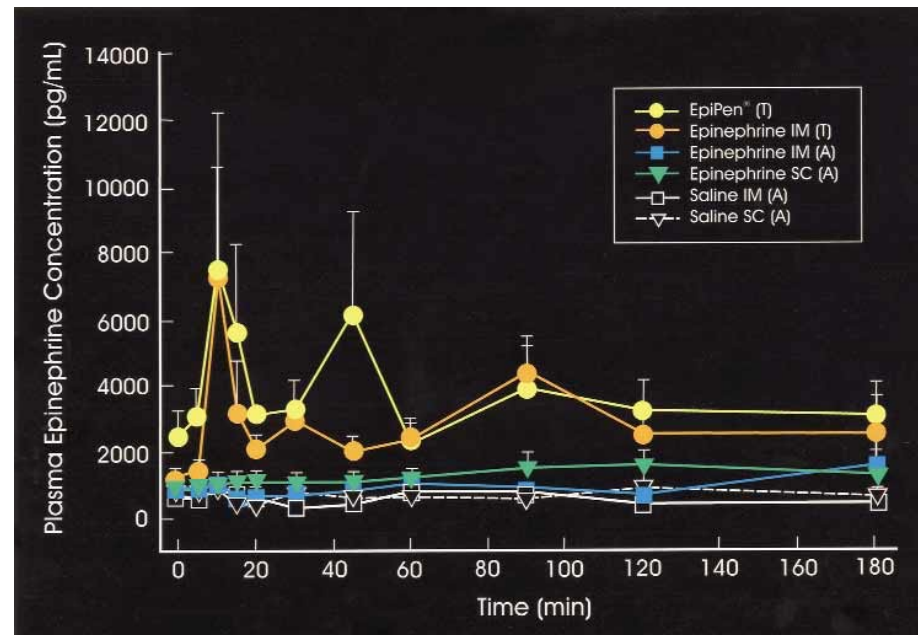


FIG 1. Mean plasma epinephrine concentrations versus time are shown after administration of an identical 0.3-mg (0.3-mL) dose of epinephrine by IM or SC injection in 2 different sites. T, Thigh; A, upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of 0.9% saline solution (0.3 mL) in the upper arm. The plasma epinephrine concentrations shown were calculated by averaging (mean \pm SEM) the epinephrine concentrations at each sampling time for each route and each site of injection.

Simons FE, Gu X, Simons KJ.
Epinephrine absorption in adults:
intramuscular versus subcutaneous
injection. J Allergy Clin Immunol. 2001
Nov;108(5):871-3.

Is IM best for anaphylaxis? (cont.)

The data do not establish that IM injection is superior to SC injection in the thigh.

In an actual clinical setting, an EpiPen injection might end up being either IM or SC,

- the patient's sex

- the body habitus

- the amount of clothing through which the needle has to travel

There are **no** reports to suggest that patients who are more likely to get autoinjected epinephrine SC, such as females and patients with large body habitus, have worse outcomes during anaphylaxis.

Why do we need alternative methods for administering epinephrine for anaphylaxis?

Bulky size and lack of carriage

It's a needle

Hesitant to use-scared

Proper training is needed

Lacerations and injuries

Cost

Lieberman JA, Oppenheimer J, Hernandez-Trujillo VP, Blaiss MS.
Innovations in the treatment of anaphylaxis: A review of recent data.
Ann Allergy Asthma Immunol. 2023 Aug;131(2):185-193.e10

How does the FDA approve alternative methods of epinephrine administration?

FDA approval pathway is called 505(b)(2)

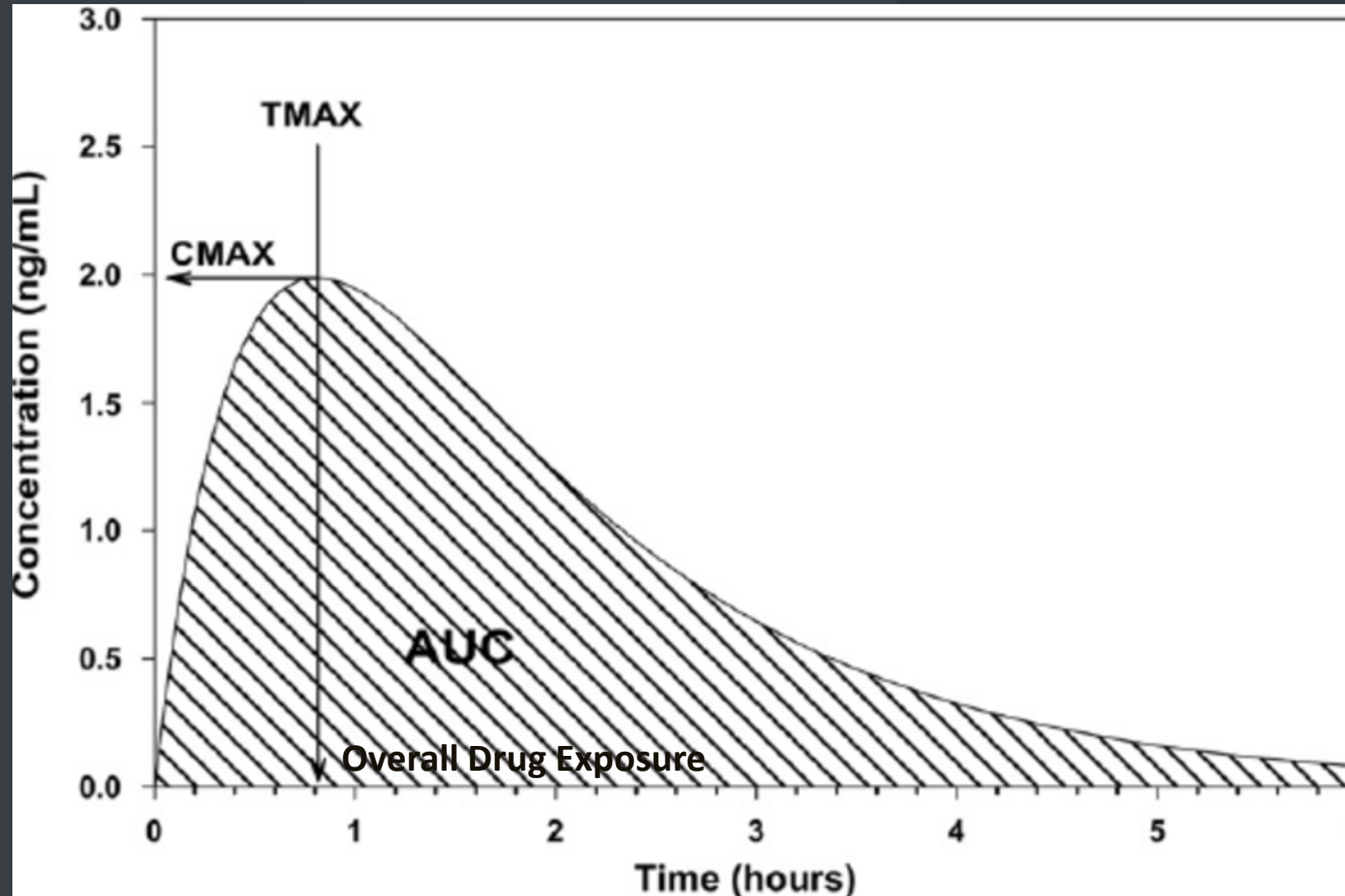
It allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant.

The performance of the device or product through animal and human pharmacokinetic (PK) and pharmacodynamic (PD) studies-”does it mimic EAI and IM Epi injection?”

PK- The study of how the body interacts with administered substances for the entire duration of exposure

PD- The study of a drug's molecular, biochemical, and physiologic effects or actions

PK measurements in Epinephrine Studies



PD measurements in Epinephrine Studies

Heart Rate

Systolic Blood Pressure

Diastolic Blood Pressure

Respiratory Rate

Which is more important PD or PK???

Intranasal Epinephrine

Vascularization of the nasal cavity which provides rapid onset action by bypassing first pass metabolism

No needle phobia

Minimal side effects to nasal delivery

Few contraindications (facial trauma, epistaxis, diseases with impaired ciliary function, e.g., cystic fibrosis).

Due to slower absorption than the IM or IV route, a higher IN dose may be necessary to achieve adequate plasma concentration.

Other types of rescue medications can be effectively administered IN, including IN naloxone in opiate overdose

ARS-1



Pharmacokinetics/pharmacodynamics of epinephrine after single and repeat administration of *neffy*, EpiPen, and manual intramuscular injection



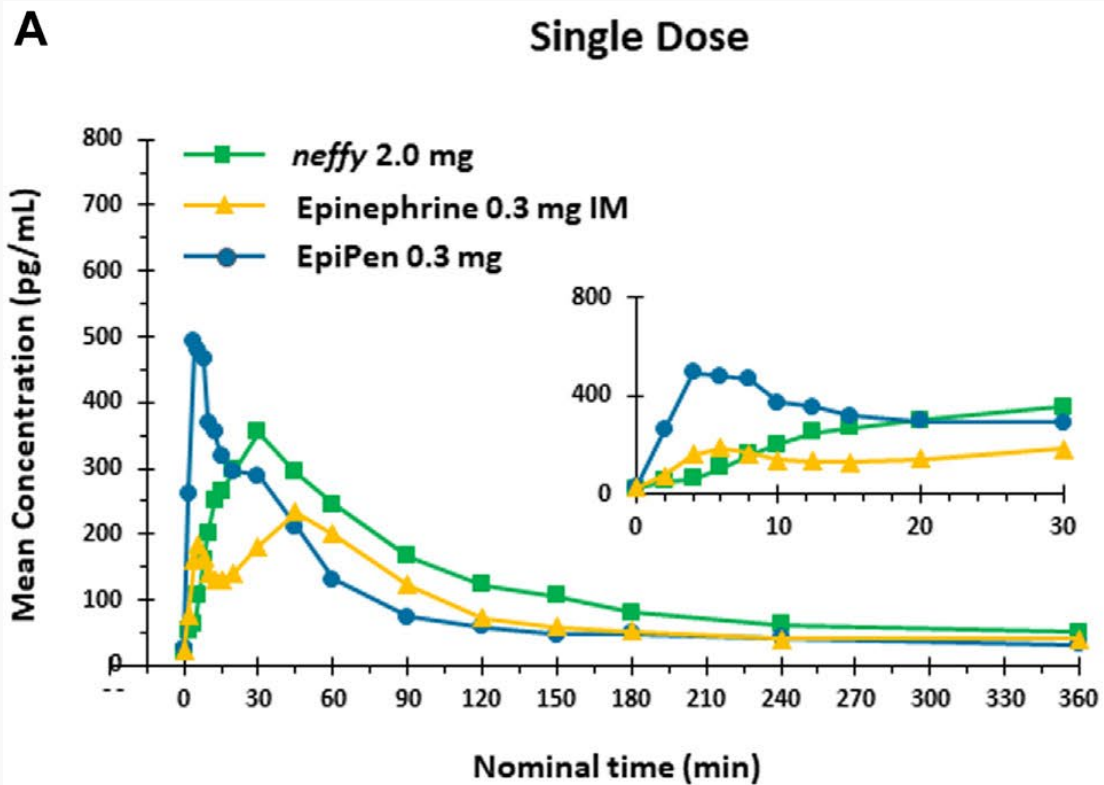
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Thomas B. Casale, MD,^a Anne K. Ellis, MD,^b Anna Nowak-Wegrzyn, MD, PhD,^c Michael Kaliner, MD,^d Richard Lowenthal, MS, MBA,^e and Sarina Tanimoto, MD, PhD^e *Tampa, Fla; Kingston, Ontario, Canada; New York, NY; Wheaton, Md; and San Diego, Calif*

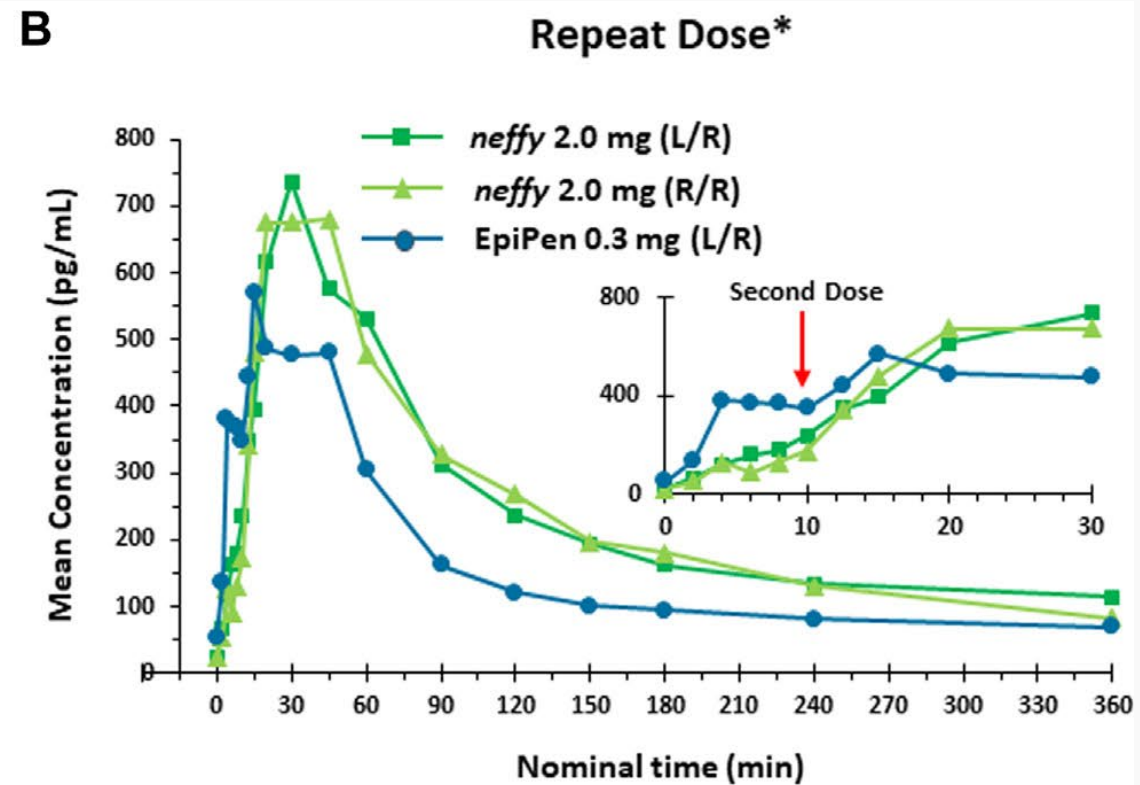
Comparative pharmacokinetics and pharmacodynamics of neffy 2.0 mg, EpiPen 0.3 mg, and manual intramuscular injection 0.3 mg.

Methods: This was a phase 1, randomized, 6-treatment, 6-period, 2-part crossover study in 59 healthy subjects.

Pharmacokinetic and pharmacodynamic parameters following single and repeat doses of epinephrine were assessed before dosing and at various postdose intervals.



*Second dose administered at 10 min.



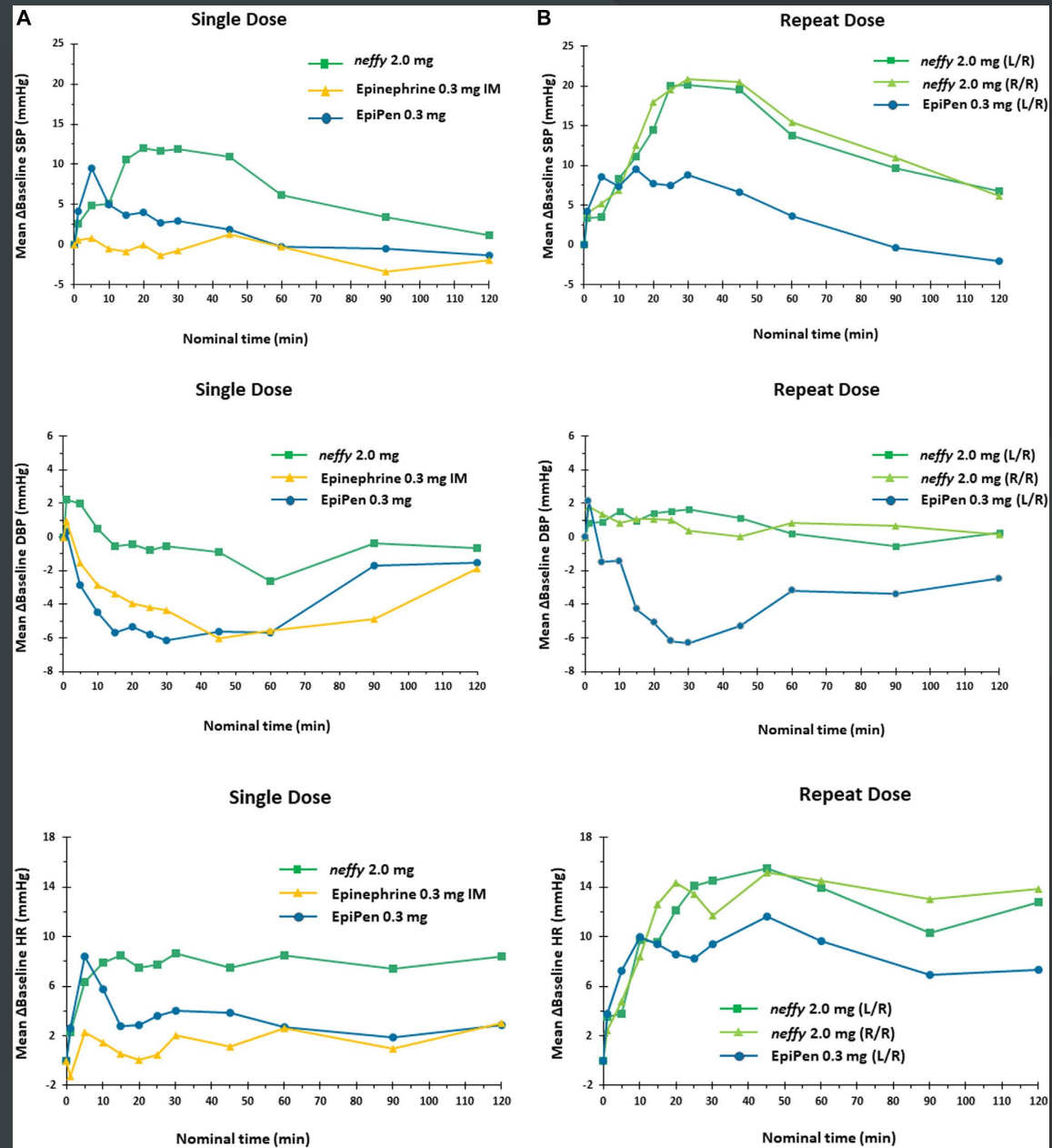


FIG 2. Mean change from baseline in SBP (top), DBP (middle), and HR (bottom) vs time. (A) Single dose. (B) Repeat dose.

neffy, Epinephrine Nasal Spray, Demonstrates a Positive Efficacy and Safety Profile for the Treatment of Allergic Reactions in Pediatric Patients at Risk of Anaphylaxis: Phase 3 Study Results

Motohiro Ebisawa, MD, PhD¹, Kento Takahashi, MD¹, Kyohei Takahashi, MD, PhD¹, Noriyuki Yanagida, MD, PhD¹, Sakura Sato, MD¹, Richard Lowenthal MSc², Sarina Tanimoto MD, PhD² Presentation ID: L33

¹Clinical Research Center for Allergy and Rheumatology, NHO Sagami National Hospital, ²ARS Pharmaceuticals, San Diego, CA, USA.

This was a Phase 3, single-period, single-dose open-label study in pediatric subjects (n = 15) who experienced allergic symptoms (Grade 2 or higher) induced by an OFC.

Grading was determined by the Severity Classification of Organ Symptoms Induced by Anaphylaxis in the Anaphylaxis Guidelines of the Japanese Society of Allergology

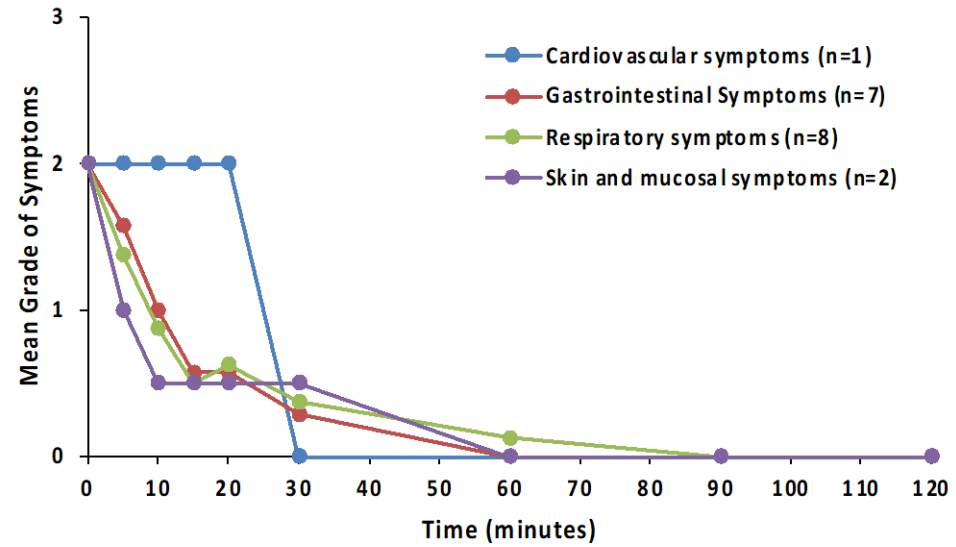
Table 1: Symptom Grading System from Anaphylaxis Guidelines¹⁰

| | 1 (Mild) | 2 (Moderate) | 3 (Severe) |
|------------------------|--|---|---|
| Skin | Localized urticaria, exanthema, wheal, pruritus | Generalized urticaria, exanthema, wheal, pruritus | - |
| | Swollen eyelid or lip | Swollen face | - |
| Gastrointestinal tract | Pruritus of the throat or oral cavity | Throat pain | - |
| | Mild abdominal pain | Moderate abdominal pain | Cramps |
| | Nausea, emesis, diarrhea | Recurrent emesis, diarrhea | Continuous emesis, loss of bowel control |
| Respiratory tract | Intermittent cough, nasal congestion, sneezing, rhinorrhea | Repetitive cough | Persistent cough, hoarseness, "barking" cough |
| | - | Chest tightness, wheezing detectable via auscultation | Audible wheezing, dyspnea, cyanosis, saturation <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest |
| Cardiovascular | - | Pale face, mild hypotension, tachycardia (increase >15 beats/min) | Hypotension, dysrhythmia, severe bradycardia, cardiac arrest |
| Neurological | Change in activity level, tiredness | Light-headedness, feeling of "pending doom," somnolence, headache | Confusion, loss of consciousness, incontinence |

neffy was administered immediately following the observation of Grade 2 symptoms. Patients weighing 15 to 30 kg received neffy 1.0 mg and patients >30 kg received neffy 2.0 mg. If symptoms remained unchanged or worsened patients were treated with IM epinephrine.

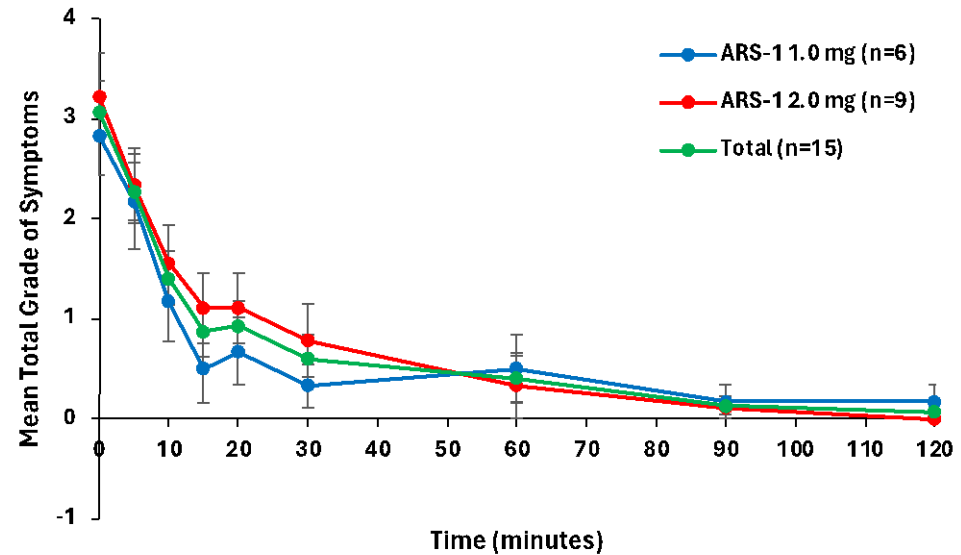
AAAAI Feb 2024

Figure 1: Time Course for the Resolution of Grade 2 Symptoms

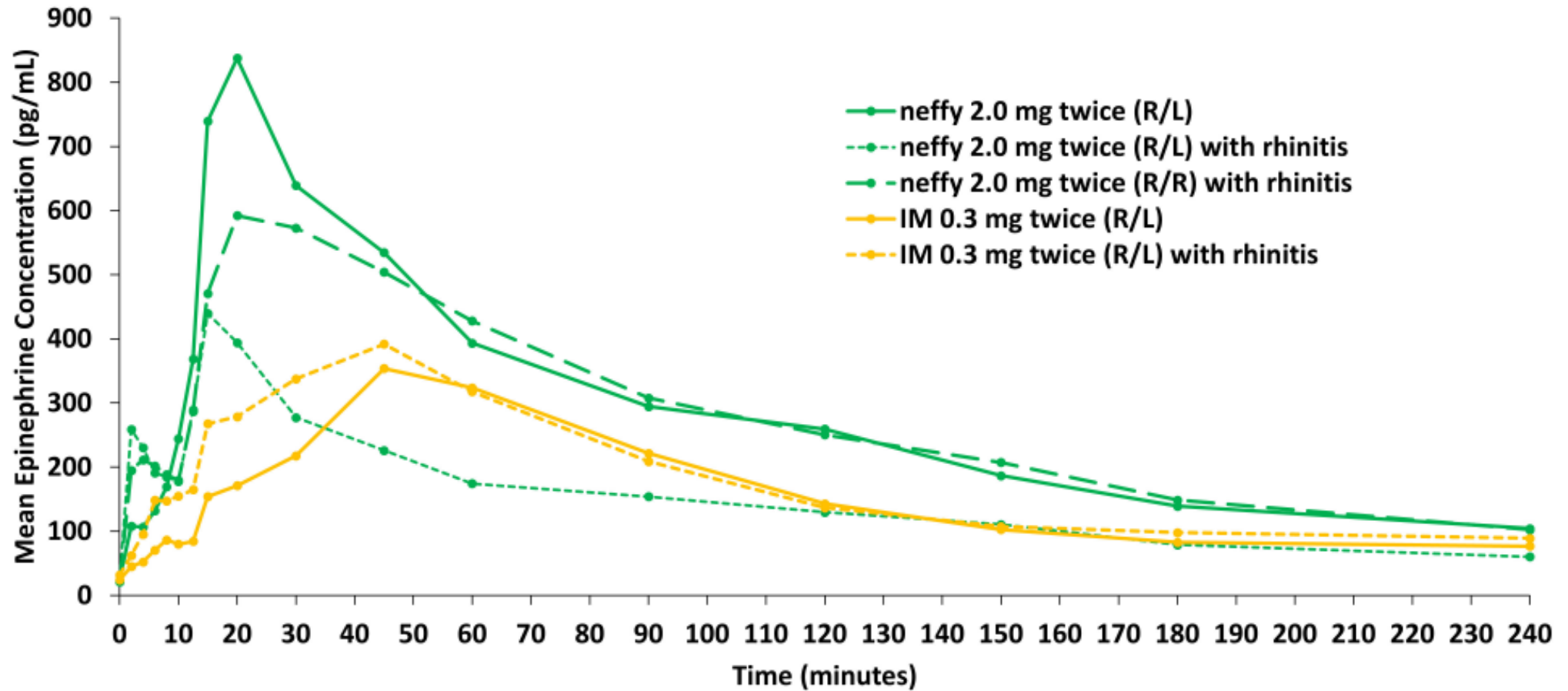


Note: The grade for cardiovascular does not have Grade 1, therefore, the next grade from Grade 2 (pale face, mild hypotension, tachycardia) was no symptom (Grade 0).

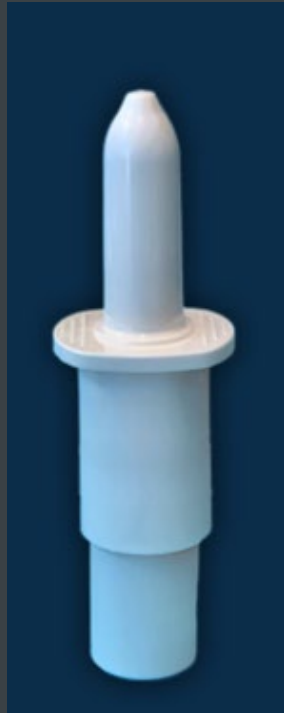
Figure 2: Time Course for Total Grade of Organ Systems




Mean Epinephrine Concentration vs. time



NDS1C



A 13.2 mg epinephrine intranasal spray demonstrates comparable pharmacokinetics, pharmacodynamics, and safety to a 0.3 mg epinephrine autoinjector

 Check for updates

David A. Dworaczyk, PhD,^a Allen L. Hunt, MD,^b Mike Di Spirito, MSc,^b Mary Lor, BSc, GrDip,^b Kenneth L. Dretchen, PhD,^c Michael J. Lamson, PhD,^d Jonathan Pollock, MSci,^b and Thelma Ward, PhD^b *Raleigh and Cary, NC; Lincoln, Neb; and Frederick, Md*

An open-label, 3-period crossover study was conducted in 116 healthy adult volunteers to assess the bioavailability of a single 13.2 mg intranasal dose of epinephrine compared to a 0.3 mg intramuscular autoinjector and a 0.5 mg manual syringe.

2 cohorts-one got 13.2 dosage in same nostril (2 puffs same nostril) and other got 13.2 dosage (1 puff in each nostril)

(J Allergy Clin Immunol Global 2024;3:100200.)

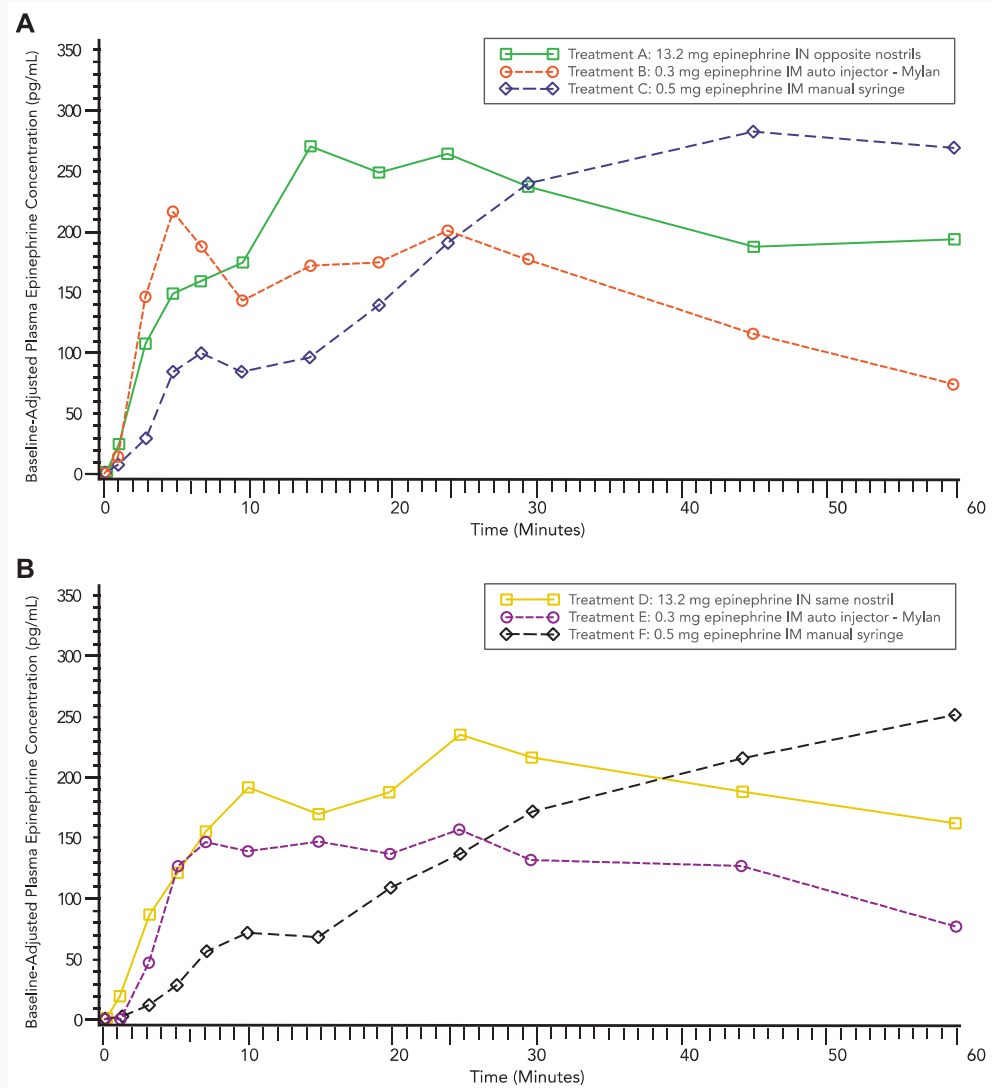


FIG 3. Median baseline-adjusted plasma epinephrine concentration–time profiles from 0 to 60 minutes. **(A)** Cohort 1. $AUC_{0-60,adj}$ P values: treatment A versus B, $P < .0001$; treatment A versus C, $P = .1643$. $C_{max0-20,adj}$ P values: treatment A versus B, $P = .1088$; treatment A versus C, $P < .0001$. **(B)** Cohort 2. $AUC_{0-60,adj}$ P values: treatment D versus E, $P = .0002$; treatment D versus F, $P = .0833$. $C_{max0-20,adj}$ P values: treatment D versus E, $P = .2102$; treatment D versus F, $P < .0001$. Treatments E and F are shifted right to ease reading.

13.2 mg INTRANASAL EPINEPHRINE TREATMENT IN CONGESTION SHOWS INCREASED BIOAVAILABILITY WITHOUT PHARMACOKINETIC AND PHARMACODYNAMIC CORRELATION

Open-label, 4-period, 4-treatment, partial crossover study

Both cohorts received the following treatments:

Period 1: 13.2 mg ENS administered by 2 consecutive sprays, with congestion induced by NAC

Periods 2 and 3: 0.3 mg epinephrine by IM autoinjector or 0.5 mg epinephrine IM by manual syringe (MS)

Period 4: 13.2 mg ENS administered by 2 consecutive sprays, without congestion

There was a washout period of 1 day between Periods 1-3 and of at least 14 days between Periods 1 and 4

Figure 1. Median baseline-adjusted plasma epinephrine concentration over time profiles after ENS with or without NAC or IM epinephrine in A) Cohort 1 (opposite nostrils) or B) Cohort 2 (same nostril).

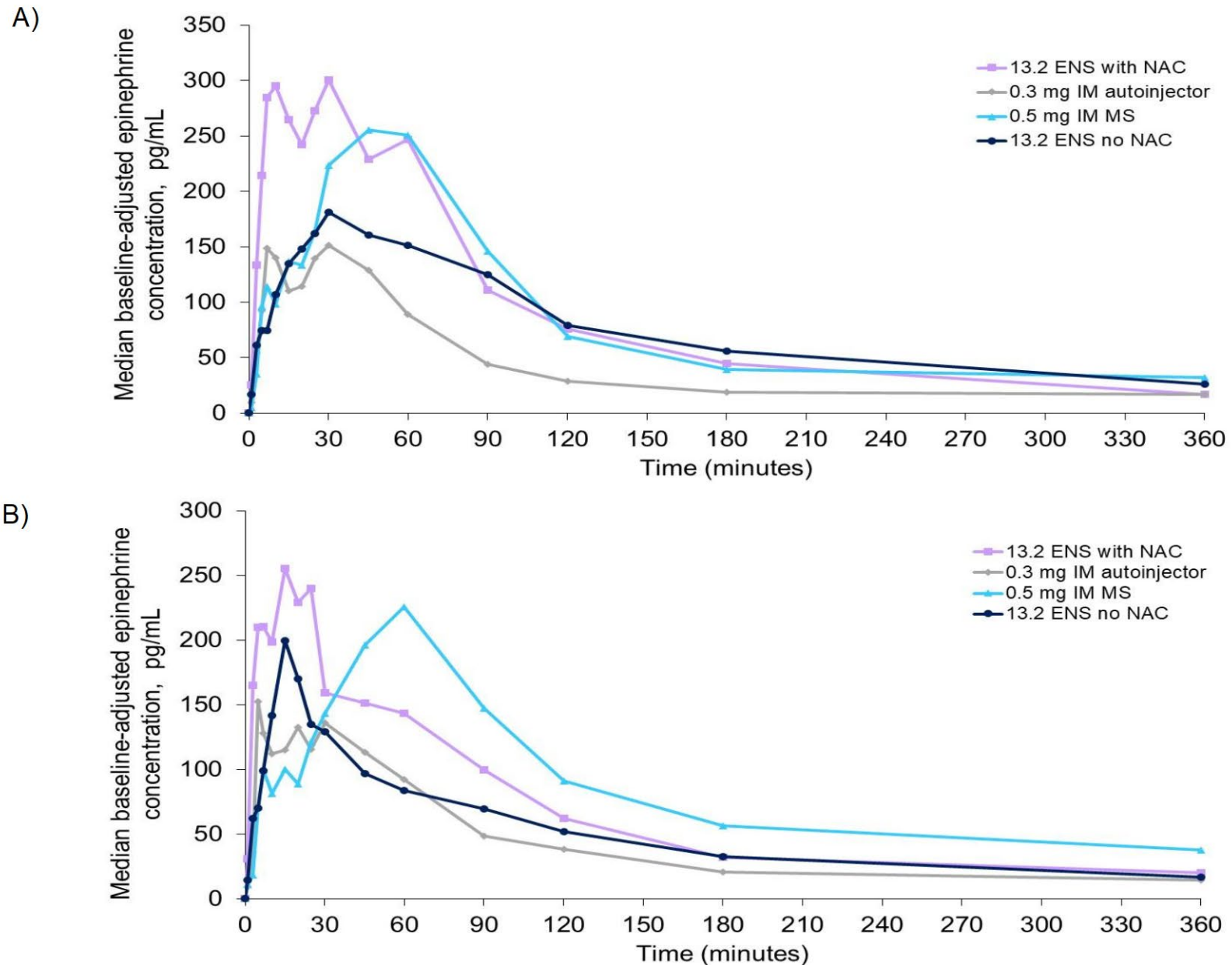


Figure 2. Proportion of participants attaining baseline-adjusted plasma epinephrine concentrations of A) 50 pg/mL, B) 100 pg/mL, and C) 200 pg/mL after ENS with or without NAC or IM epinephrine in Cohort 1 (opposite nostrils) or Cohort 2 (same nostril).

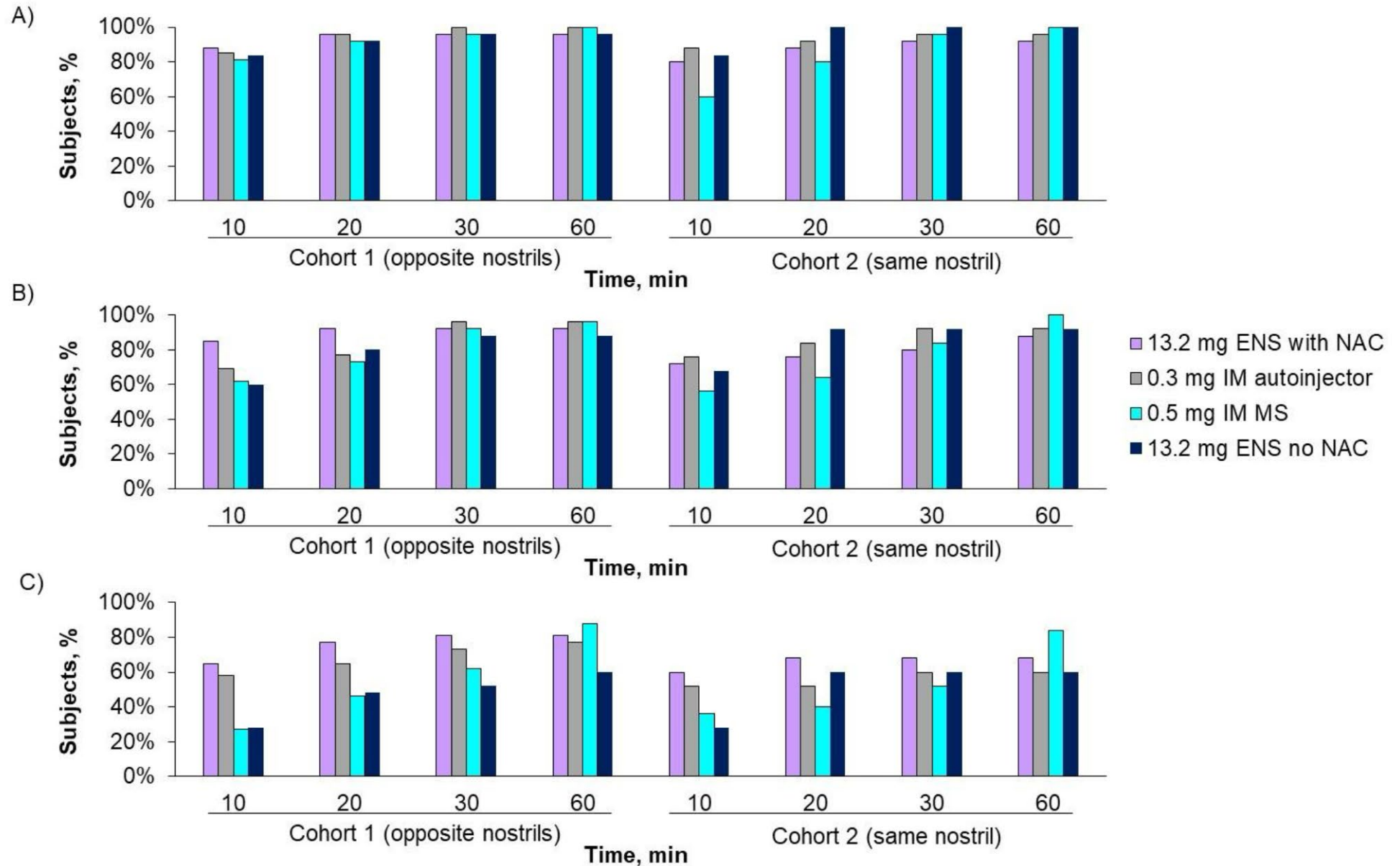


Table 4. Treatment-related adverse events (TEAE) in subjects receiving 13.2 mg ENS with or without NAC, IM autoinjector, or IM MS in Cohort 1 (Opposite Nostrils) and Cohort 2 (Same Nostril).

| Subjects with TEAE, n (%) | Cohort 1 (Opposite Nostrils) N=26 | | | | Cohort 2 (Same Nostril) N=25 | | | |
|---------------------------|--------------------------------------|-----------------|--------|-------------------------|---------------------------------|-----------------|--------|-------------------------|
| | 13.2 mg ENS with NAC | IM autoinjector | IM MS | 13.2 mg ENS without NAC | 13.2 mg ENS with NAC | IM autoinjector | IM MS | 13.2 mg ENS without NAC |
| Any TEAE | 14 (54) | 4 (15) | 7 (27) | 16 (64) | 11 (44) | 4 (16) | 5 (20) | 12 (48) |
| Headache | 6 (23) | 0 | 1 (4) | 4 (16) | 9 (36) | 0 | 3 (12) | 8 (32) |
| Nausea | 4 (15) | 1 (4) | 0 | 8 (32) | 4 (16) | 0 | 0 | 3 (12) |
| Oropharyngeal pain | 4 (15) | 1 (4) | 0 | 1 (4) | 1 (4) | 0 | 0 | 0 |
| Vomiting | 3 (12) | 0 | 0 | 6 (24) | 4 (16) | 0 | 0 | 1 (4) |
| Nasal discomfort | 2 (8) | 0 | 0 | 6 (24) | 0 | 0 | 0 | 0 |
| Upper abdominal pain | 1 (4) | 0 | 0 | 3 (12) | 3 (12) | 0 | 0 | 3 (12) |
| Injection site pain | 0 | 3 (12) | 3 (12) | 0 | 0 | 1 (4) | 1 (4) | 0 |

AE, adverse event; ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge.

Poster at AAAAI 2024 –PK/PD Data IN Epi vs IM Epi in 4 pooled studies

Figure 1. Median baseline-adjusted plasma epinephrine concentration – time profiles from 0-360 minutes

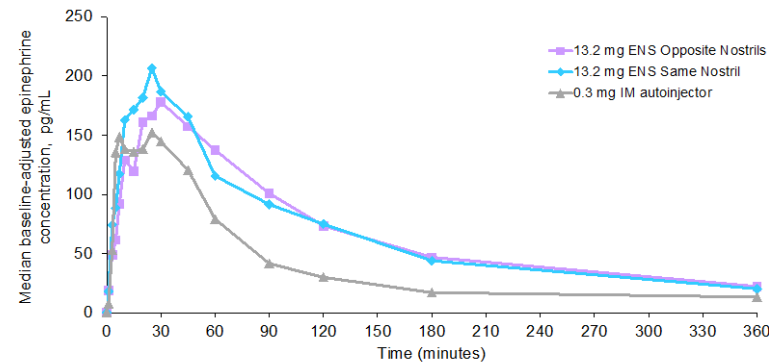
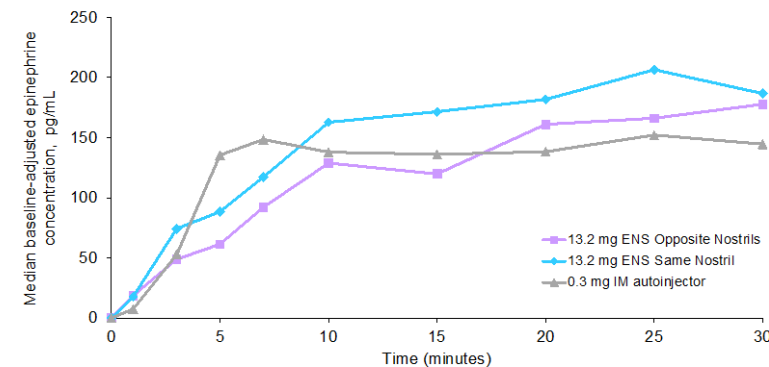
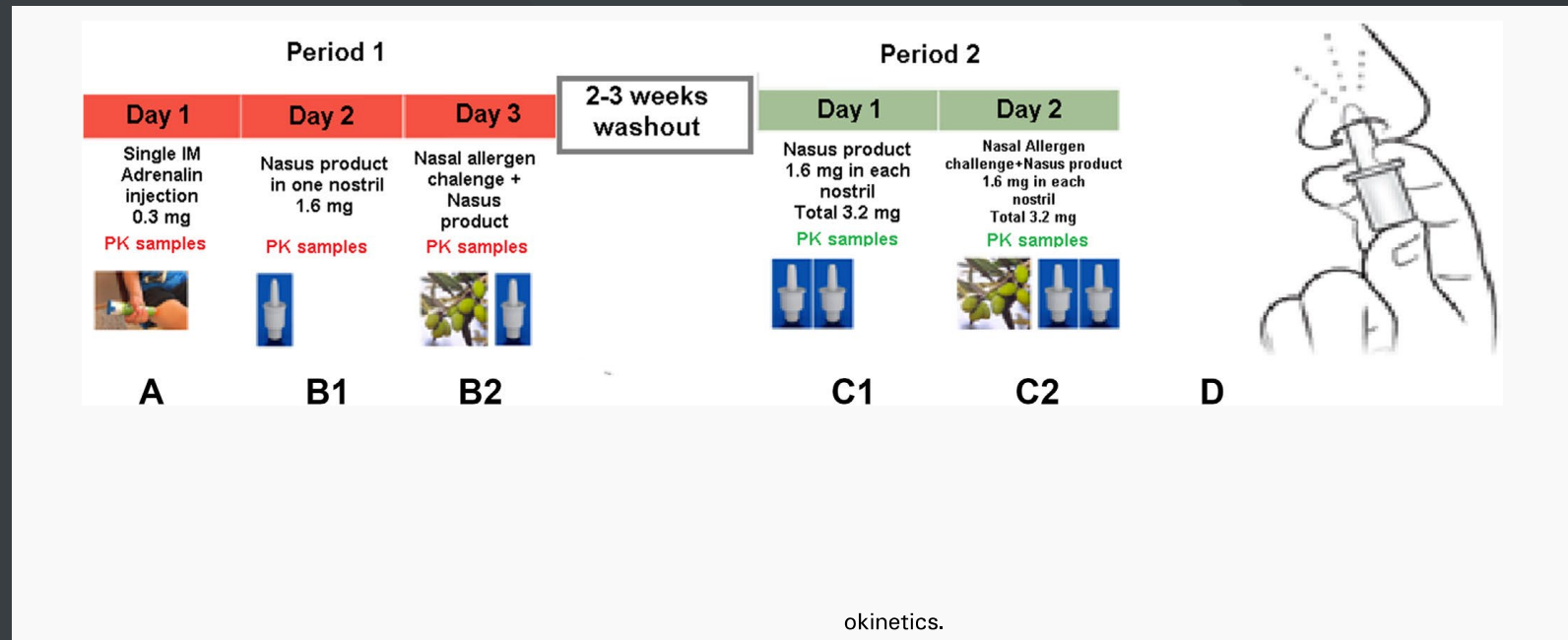


Figure 2. Median baseline-adjusted plasma epinephrine concentration – time profiles from 0-30 minutes



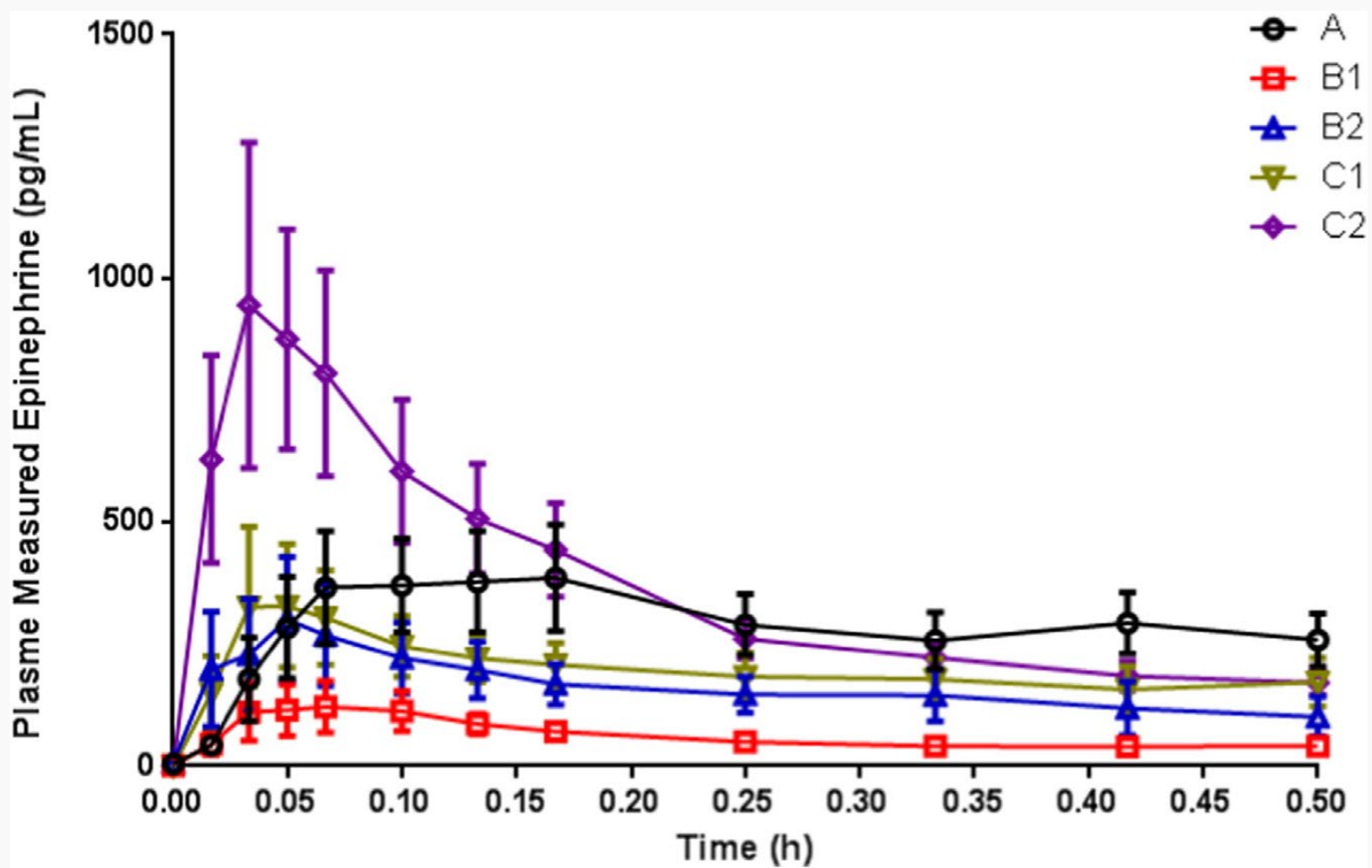
Dry Powder Intranasal Epinephrine

An open-label trial was performed in 12 adults with seasonal allergic rhinitis without asthma. Epinephrine pharmacokinetics, pharmacodynamics, and safety were compared between FMXIN002 (1.6 mg and 3.2 mg) administered intranasally with/without a nasal allergen challenge and IM (0.3 mg) EpiPen.



okinetics.

Tal Y, Ribak Y, Rubin L, et al. Fast Acting, Dry Powder, Needle-Free, Intranasal Epinephrine Spray: A Promising Future Treatment for Anaphylaxis. J Allergy Clin Immunol Pract. 2023 Oct;11(10):3047-3054.



Sublingual Epinephrine

Like IN epi, sublingual epi allows medications to bypass first pass metabolism of the liver

One problem could be the bitter taste of epinephrine

Tablets and films

Sublingual Film- AQST-109

AQST-109 is a polymer matrix-based epinephrine prodrug administered as a sublingual film that is applied under the tongue for the rapid delivery of epinephrine.

The product is similar in size to a postage stamp, weighs less than an ounce.

Dissolves on contact with no water or swallowing required for administration.

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

034

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

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

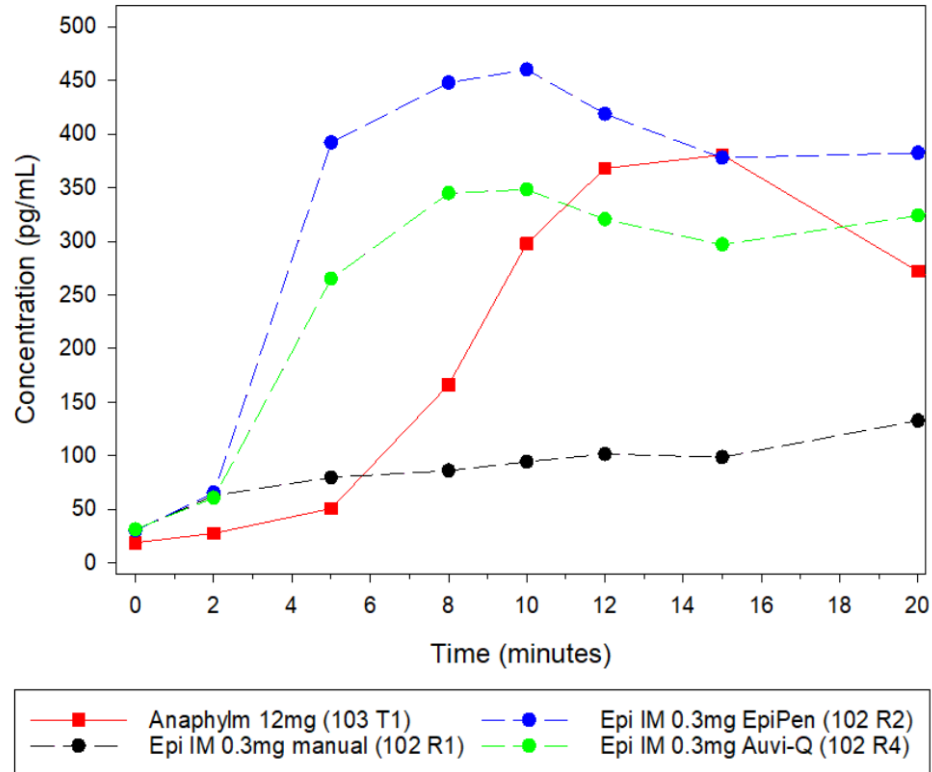


Table 1: Epinephrine PK Parameters by Treatment

| 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 (%).

Figure 2: Median Change from Baseline in Systolic Blood Pressure

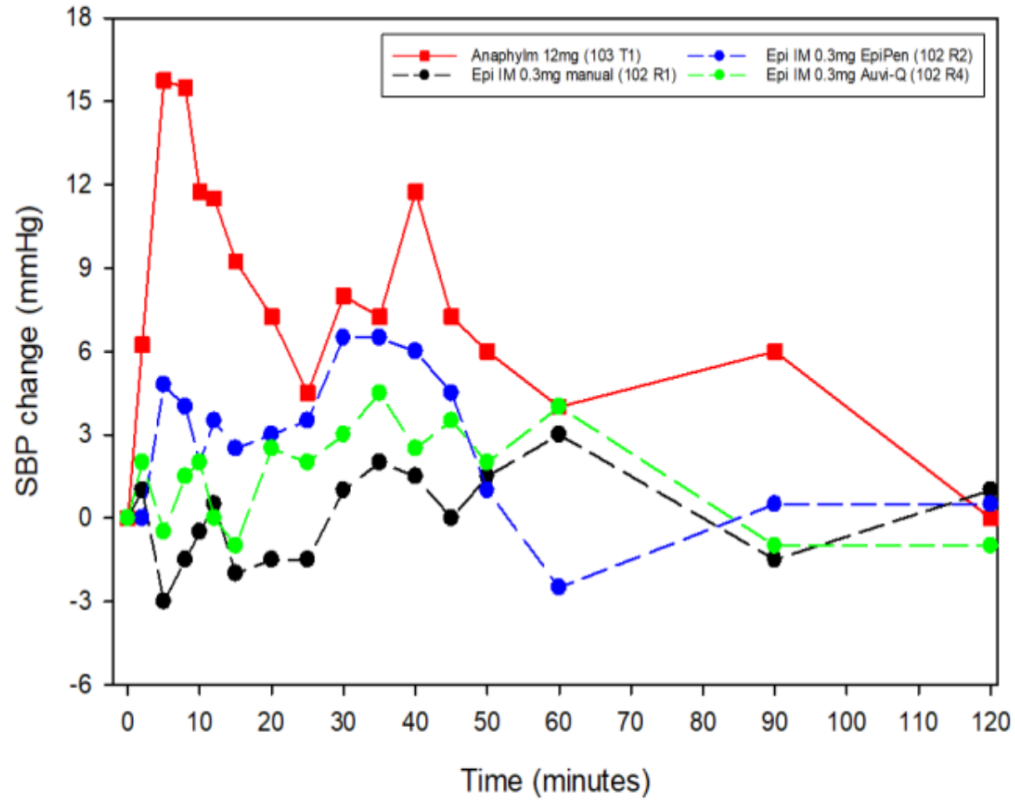
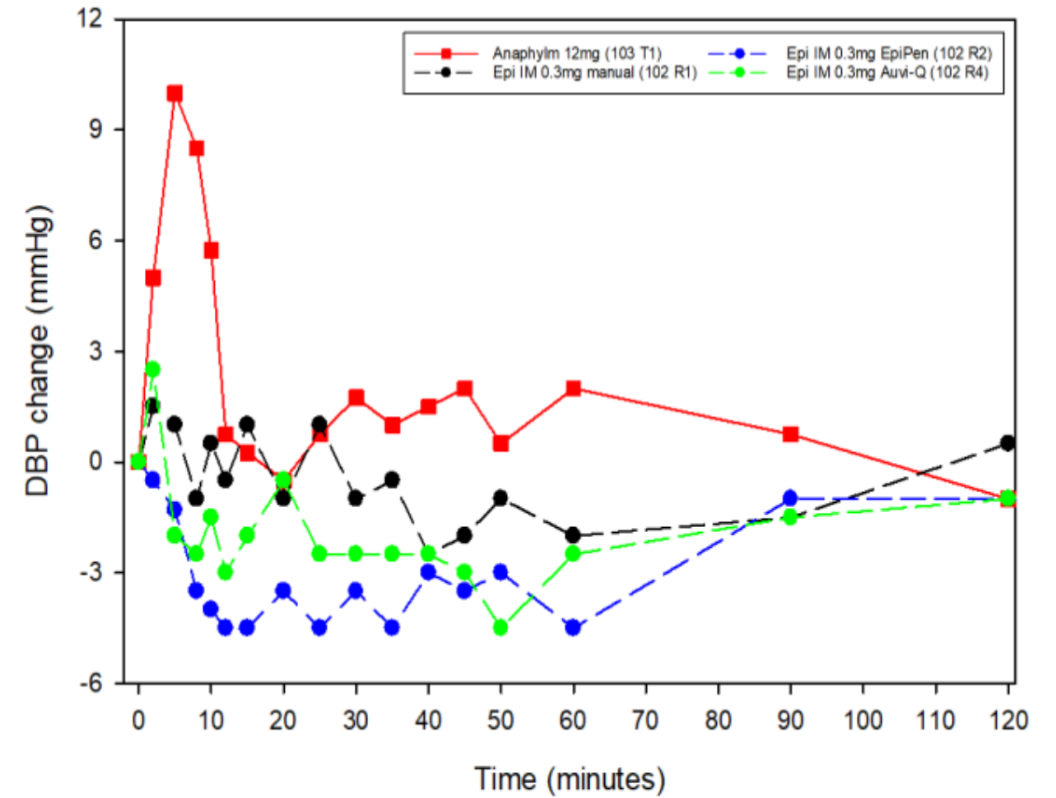


Figure 3: Median Change from Baseline in Diastolic Blood Pressure



Inhaled Epinephrine

Is there a role for inhaled epinephrine in anaphylaxis?

OTC inhaled epinephrine has 0.125 mg per puff

Data suggests that one would need to take at least 20 puffs to possibly have a therapeutic effect

In 1991, Mellen show in 9 adults that 20 puffs (0.150 mg per puff) had rapid peak epinephrine effect at one minute

In 2000, Simons et al. looked at children but levels of epinephrine were no higher than placebo probably due to difficulty for children to do 1—20 puffs and the taste of the inhalations

Schlegel et al. warned about the role of inhaled epinephrine in anaphylaxis

- Variable inhalation techniques

- Severe gastrointestinal adverse effects

- Risk of hyperventilation

Mellem H, Lande K, et. al. Br J Clin Pharmacol. 1991;31(6):677–681.

Simons FE, et. al. Pediatrics. 2000 Nov;106(5):1040-4.

Schlegel C, Fux R et. Al. J Dtsch Dermatol Ges. 2009;7(5):420–426.

Shaker MS, Golden DBK et. Al. Ann Allergy Asthma Immunol. 2023 Dec 9:S1081-1206(23)01488-6.

Better Autoinjectors

Windgap Medical

ANDIPEN

Compact Dual Chamber

The ANDIPEN is a wet/dry dual-chamber autoinjector built to drastically improve temperature resilience and shelf lives of medications traditionally offered and stored in liquid form. The ANDI® Platform is the basis for our epinephrine product, currently in pre-production in partnership with ALK -Abelló.

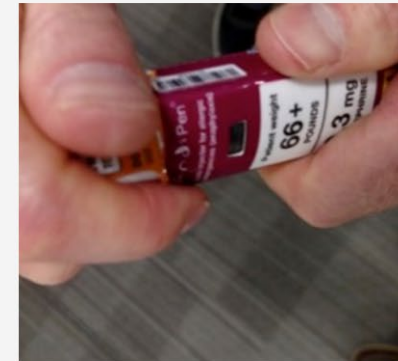
KEY FEATURES

- Automatic mixing
- Small molecule
- Rapid dissolution
- <0.3mL delivered dose volume

Accurate Dosing in 3 Easy Steps



1. Grab



2. Twist



3. Inject

Zeneo-needle free, prefilled, single use autoinjector

The device consists of a specially designed glass tube that can withstand high pressure in combination with a propellant based on a nitrocellulose chemical reaction.

When activated, the device propels the drug under high pressure through the skin into the bloodstream without the need for a needle.



Conclusions

We have come a long way since the first medical use of epinephrine over 120 years ago.

Although IM epinephrine is highly effective, but our present autoinjectors carry lots of issues for our patient population leading to underuse.

Alternative forms of administration are very promising with PK and PD data in the range of autoinjectors and IM syringe epinephrine.

If and when approved, clinical data will show the true efficacy and side effect profile of these alternative forms.