Epinephrine: Alternate routes of administration

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Upon completion of this learning activity, participants should be able to:

Paraphrase a brief history of epinephrine

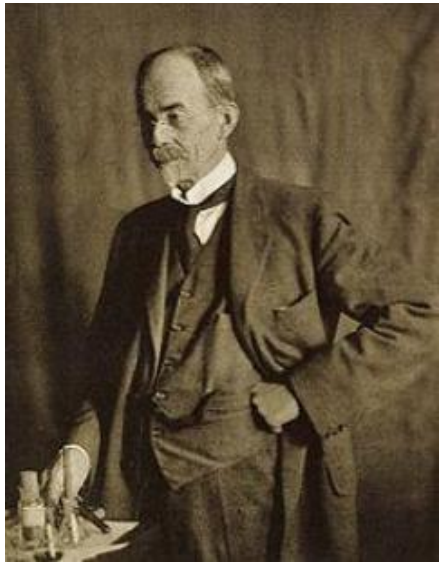
Explain how FDA process to approve new routes of administration of epinephrine

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

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 articles[1] are retained. The salts of epinephrin secured in this way possess but little physiological

Jeffrey Aronson: When I Use a Word . . . Adrenaline and epinephrine
January 26, 2018. BMJ Opinion

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 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.

Arthur G. Epinephrine: a short history. Lancet Respir Med. 2015 May;3(5):350-1.

A Brief History of Epinephrine (cont.)

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).

Jeffrey Aronson: When I Use a Word . . . Adrenaline and epinephrine. BMJ Opinion January 26, 2018

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

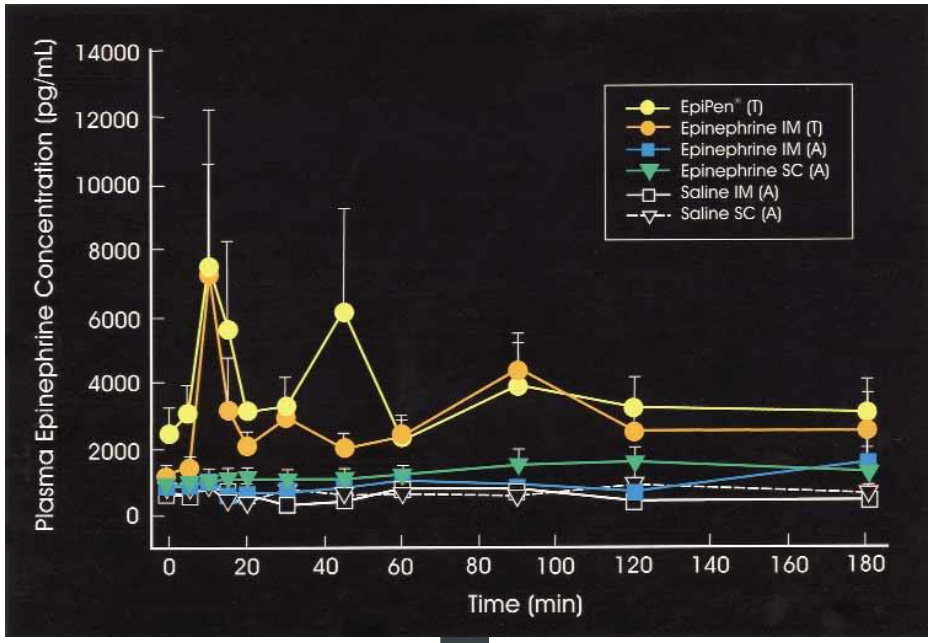


FIG 1. Mean plasma epinephrine concentrations versus time are shown after administration of an identical 0.3-mg (0.3-mL) dose of epinephrine by IM or SC injection in 2 different sites. *T,* Thigh; *A,* upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of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

Chowdhury BA, Meyer RJ. Intramuscular versus subcutaneous injection of epinephrine in the treatment of anaphylaxis. J Allergy Clin Immunol. 2002 Apr;109(4):720

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)**

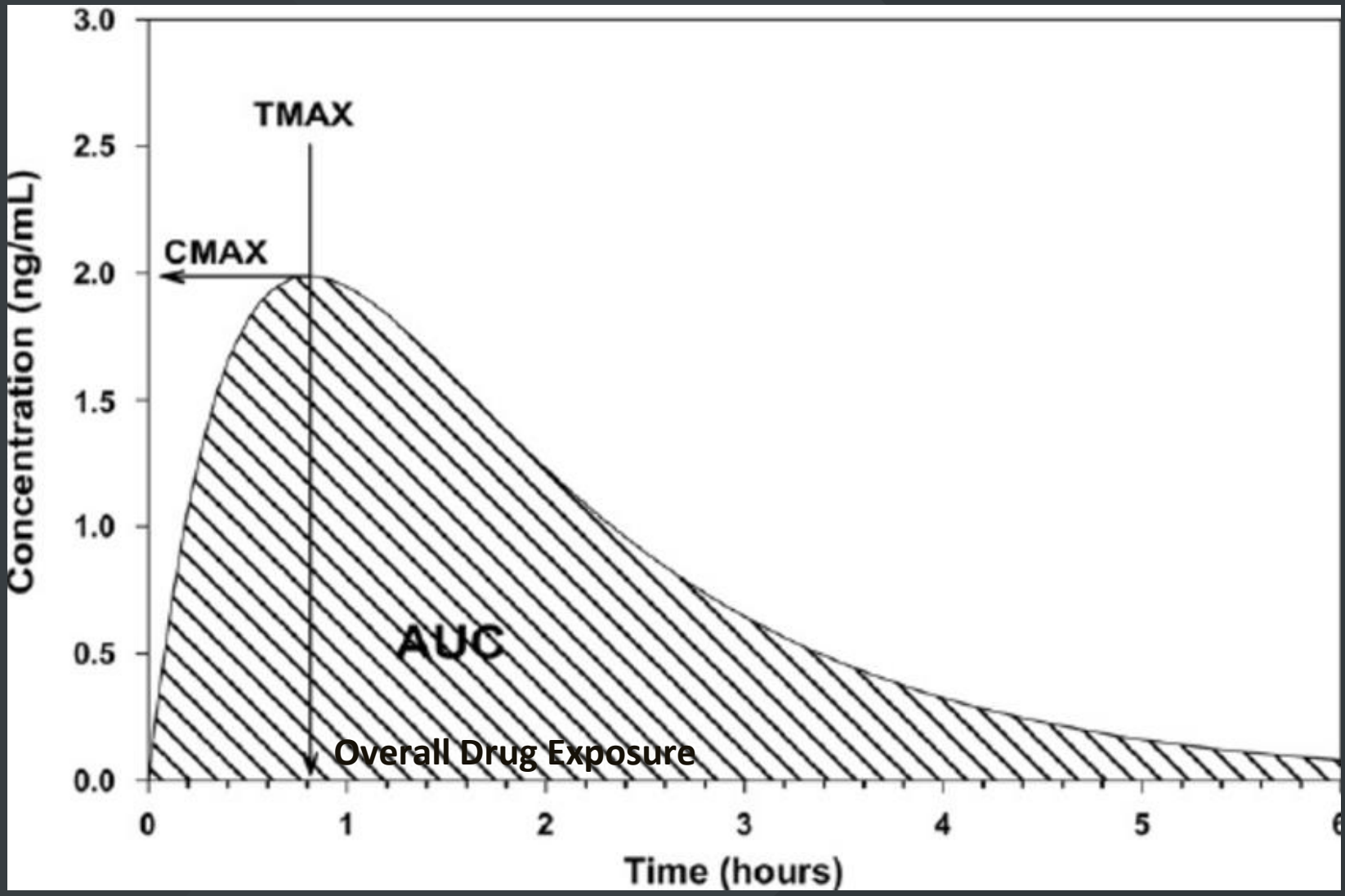
- It allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant.

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

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

Boswell B, Rudders SA, Brown JC. Emerging Therapies in Anaphylaxis: Alternatives to Intramuscular Administration of Epinephrine. Curr Allergy Asthma Rep. 2021 Mar 5;21(3):18.

ARS-1

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

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.

J Allergy Clin Immunol. 2023 Dec;152(6):1587-1596

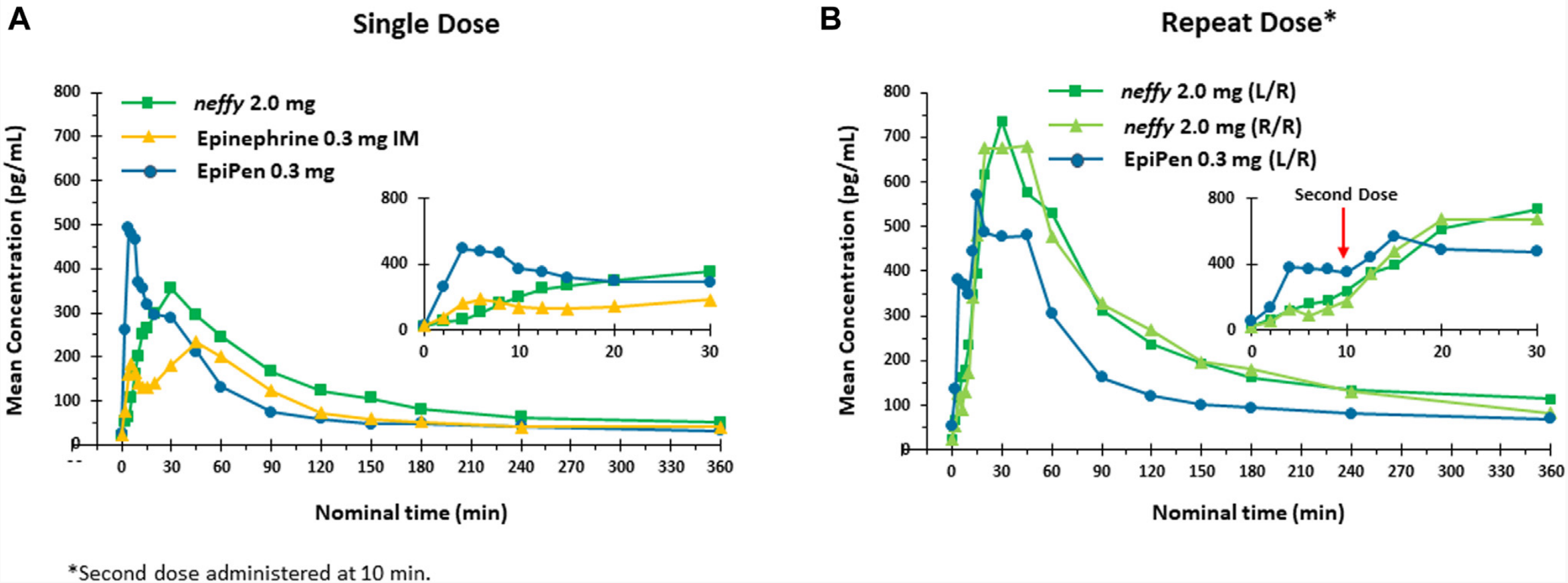


FIG 1. Mean epinephrine concentration-time profiles. **(A)** Single dose. **(B)** Repeat dose.

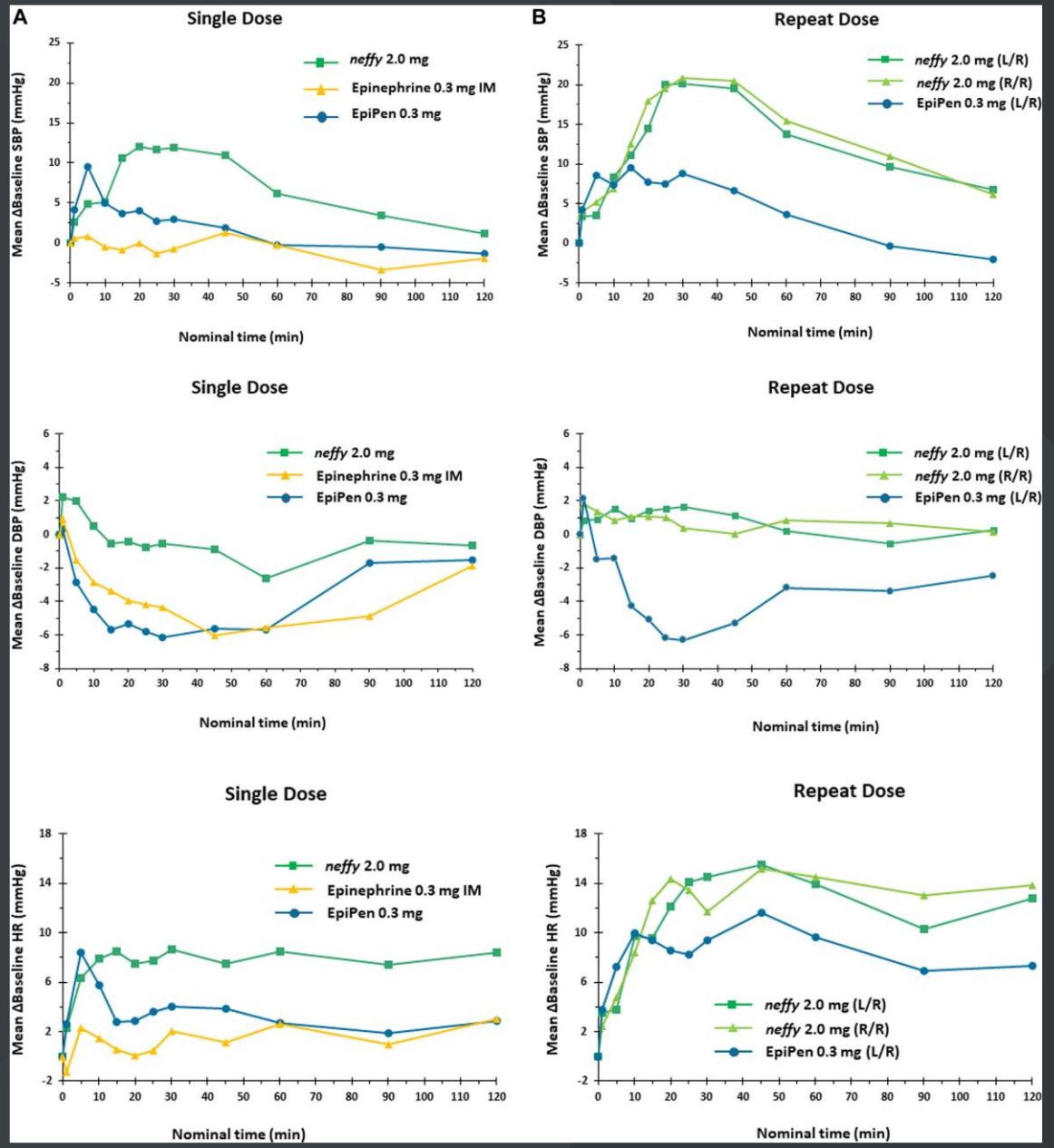


FIG 2. Mean change from baseline in SBP *(top)*, DBP *(middle)*, and HR *(bottom)* vs time. **(A)** Single dose. **(B)** Repeat dose.

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, PhD[1], Kento Takahashi, MD[1], Kyohei Takahashi, MD, PhD[1], Noriyuki Yanagida, MD, PhD[1], Sakura Sato, MD[1], Richard Lowenthal MSc[2], Sarina Tanimoto MD, PhD[2]

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

Presentation ID: L33

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

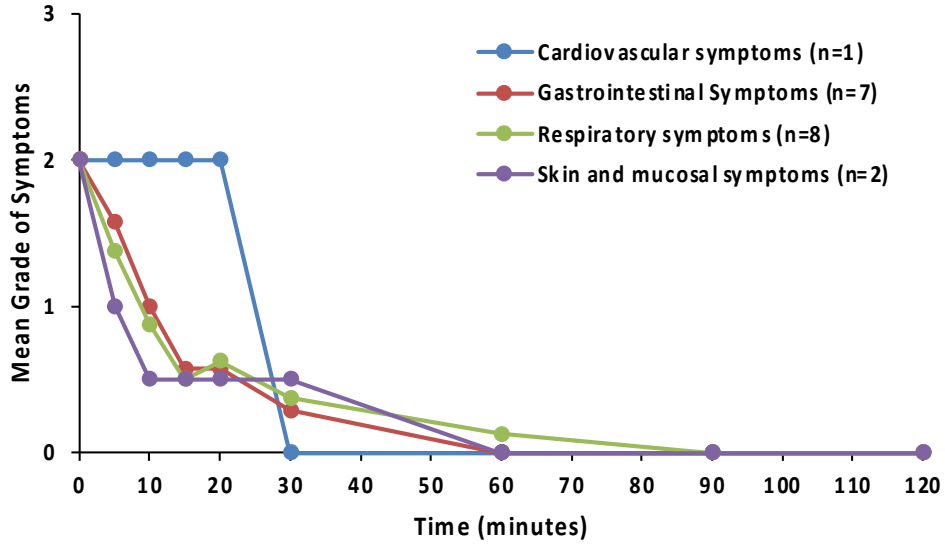
Table 1: Symptom Grading System from Anaphylaxis Guidelines[10]

	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 ≤30 kg received ***neffy*** 1.0 mg and patients [illegible] ***neffy*** 2.0 mg. If symptoms remained unchanged or worsened patients were treated with IM epinephrine.

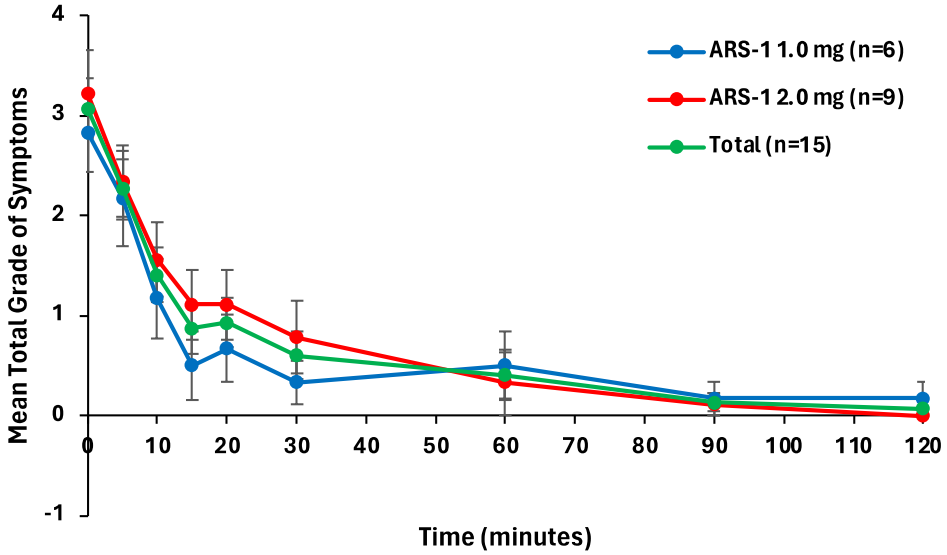
AAAAI Feb 2024

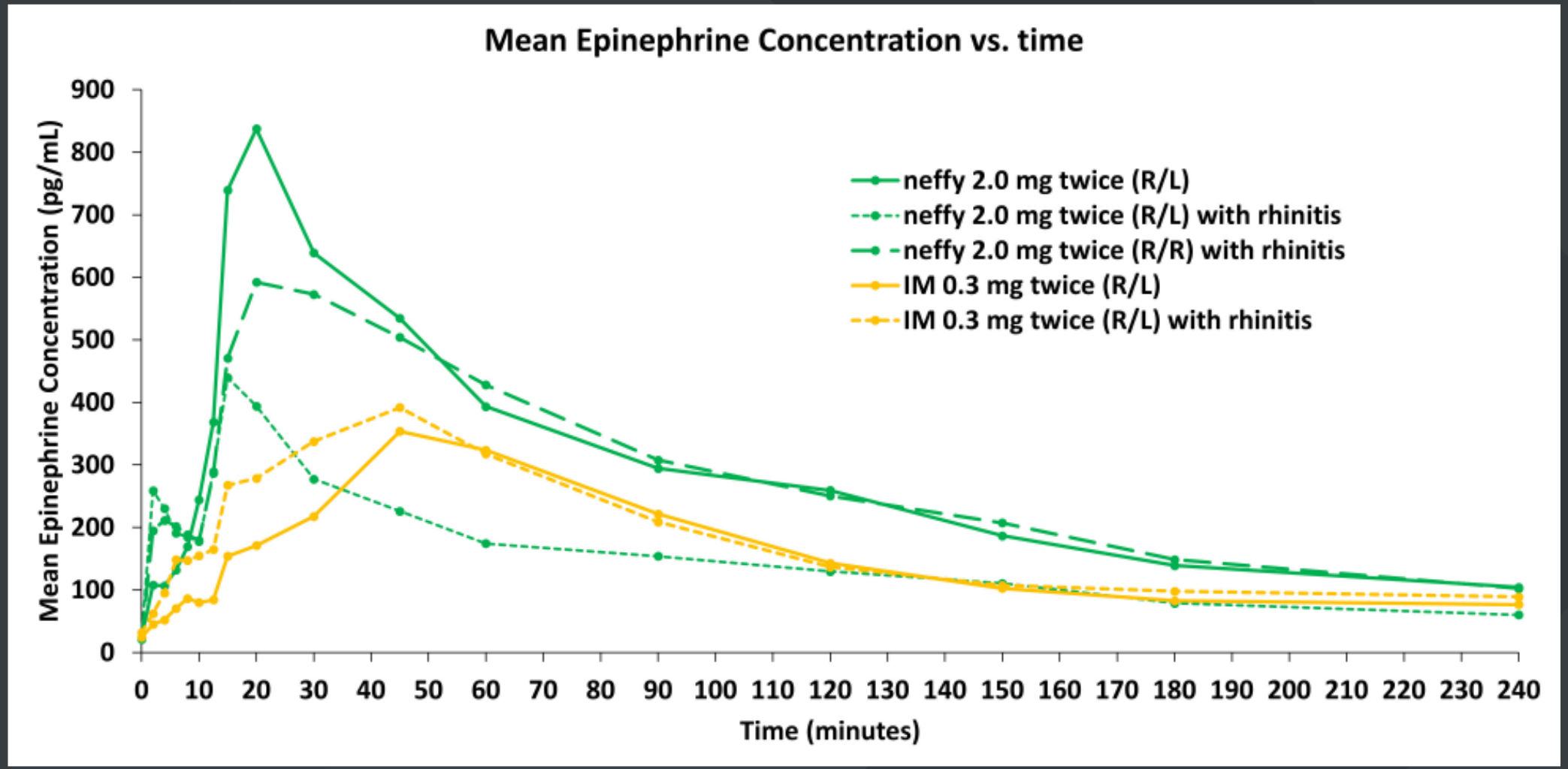
Figure 1: Time Course for the Resolution of Grade 2 Symptoms



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





Press Release ARS Pharma Feb 20, 2024

NDS1C

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

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.)

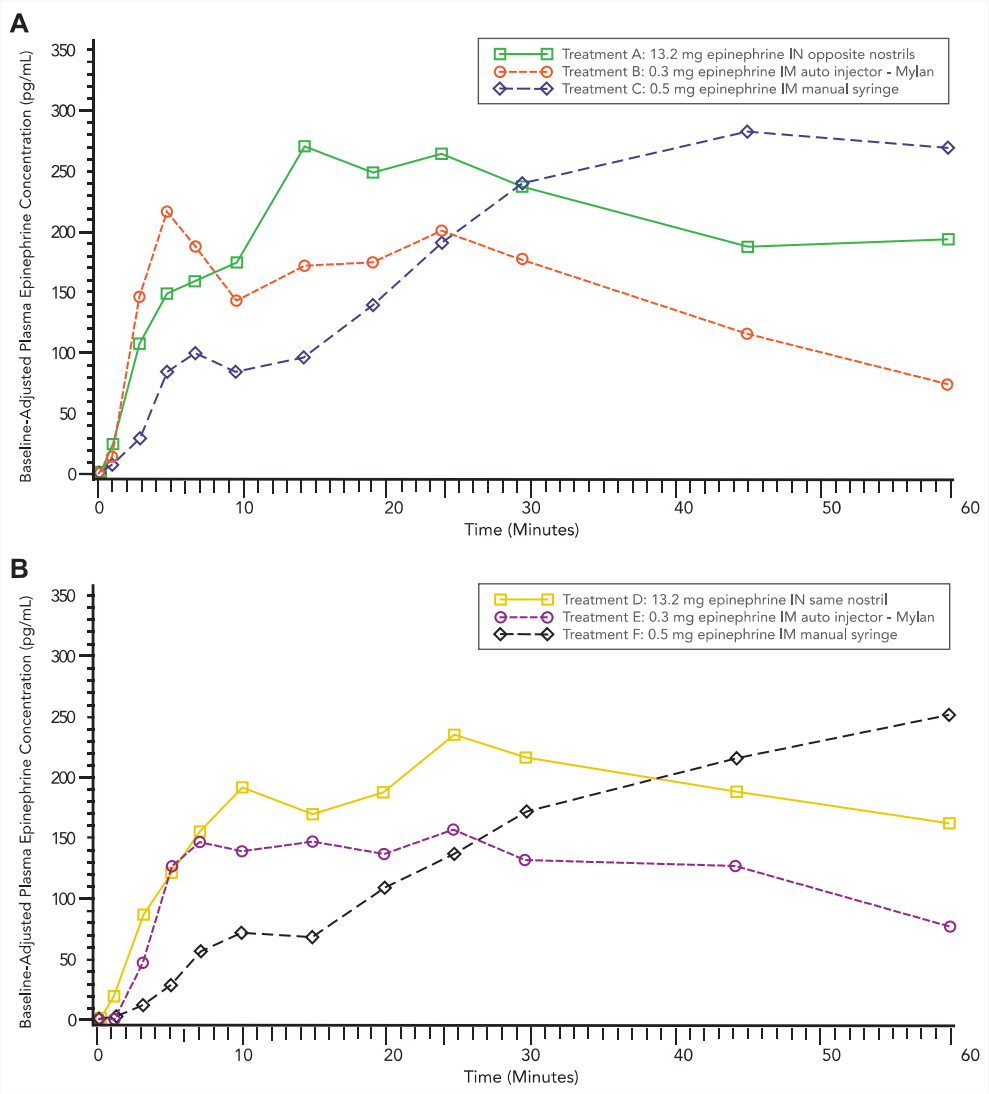


FIG 3. Median baseline-adjusted plasma epinephrine concentration–time profiles from 0 to 60 minutes. **(A)** Cohort 1. $AUC_{0\text{-}60,adj}$ *P* values: treatment A versus B, $P < .0001$; treatment A versus C, $P = .1643$. $C_{max0\text{-}20,adj}$ *P* values: treatment A versus B, $P = .1088$; treatment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

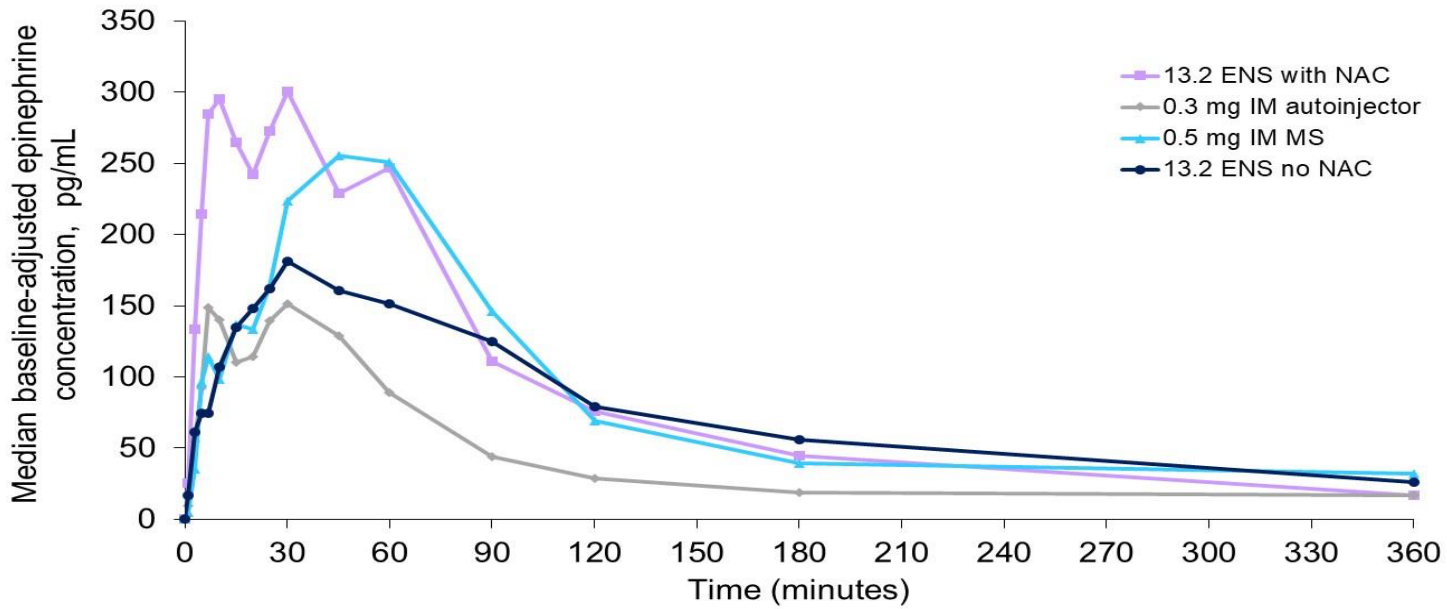
Period 4: 13.2 mg ENS administered by 2 consecutive sprays, without congestion

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

Poster at ACAAI Anaheim 2023

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

A)



B)

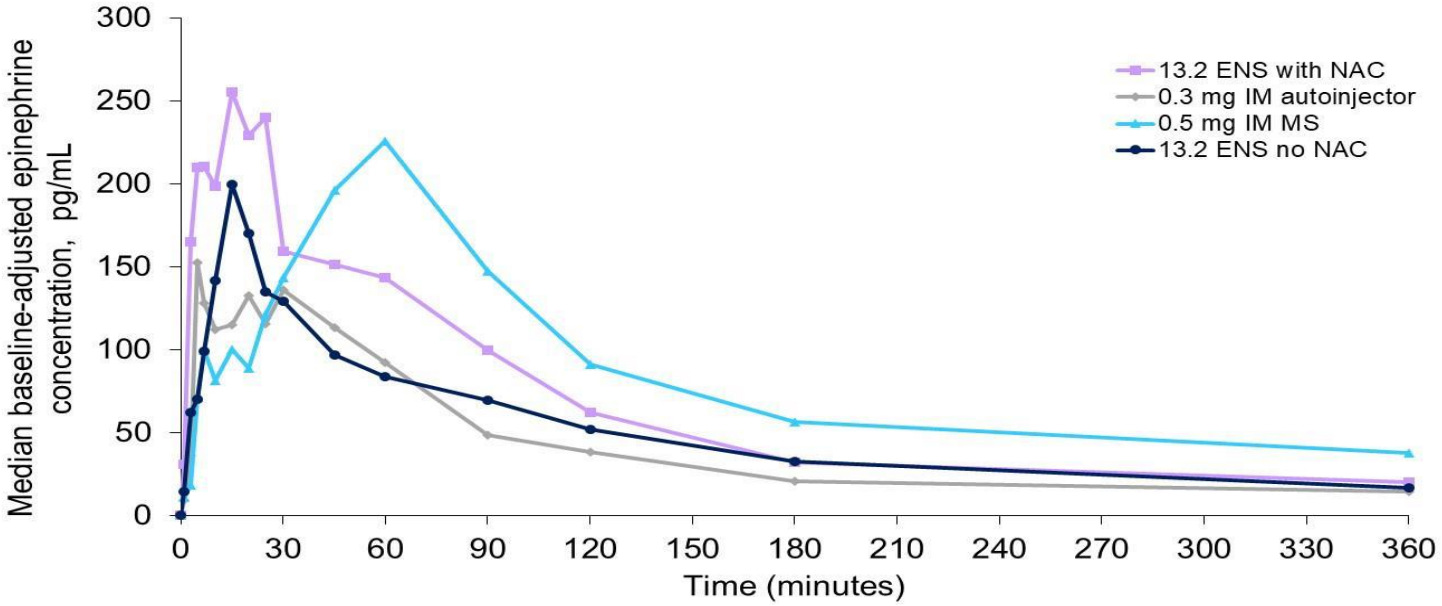
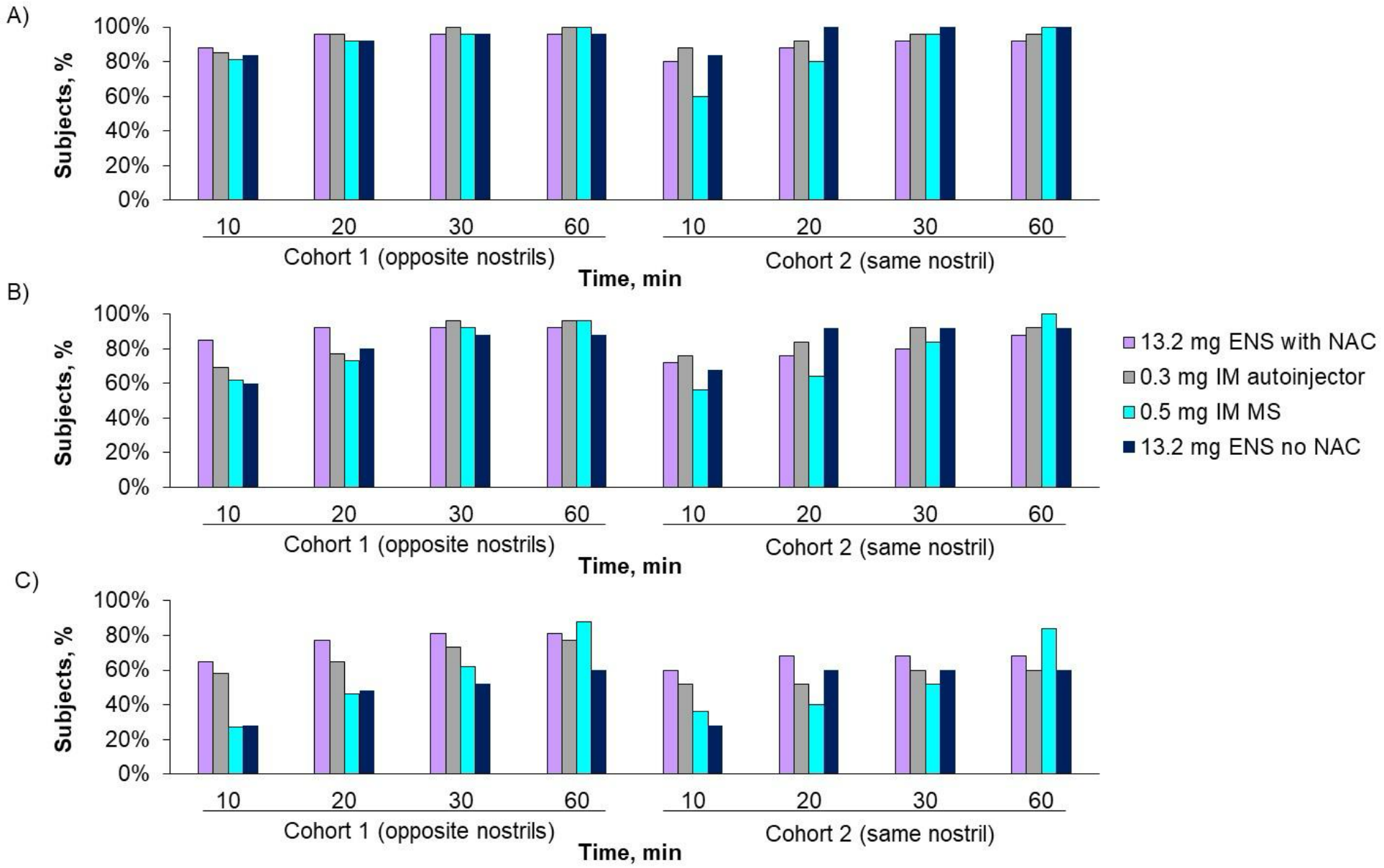


Figure 2. Proportion of participants attaining baseline-adjusted plasma epinephrine concentrations of A) 50 pg/mL, B) 100 pg/mL, and C) 200 pg/mL after ENS with or without NAC or IM epinephrine in Cohort 1 (opposite nostrils) or Cohort 2 (same nostril).



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

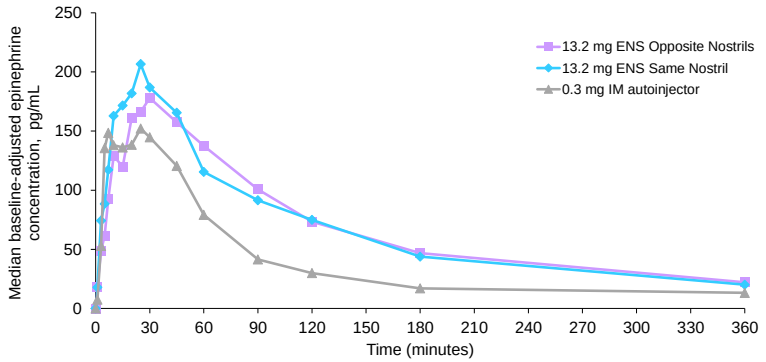
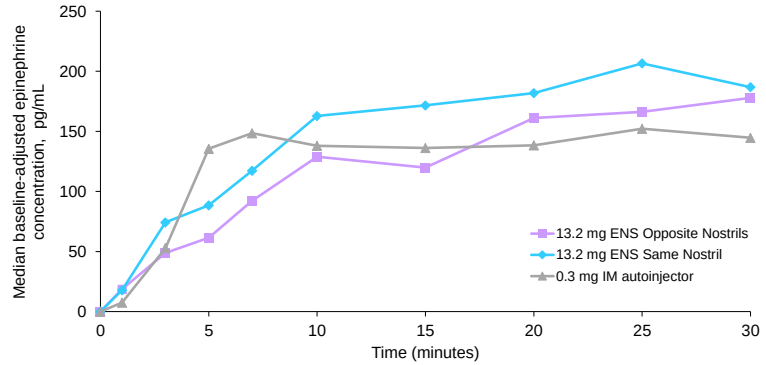
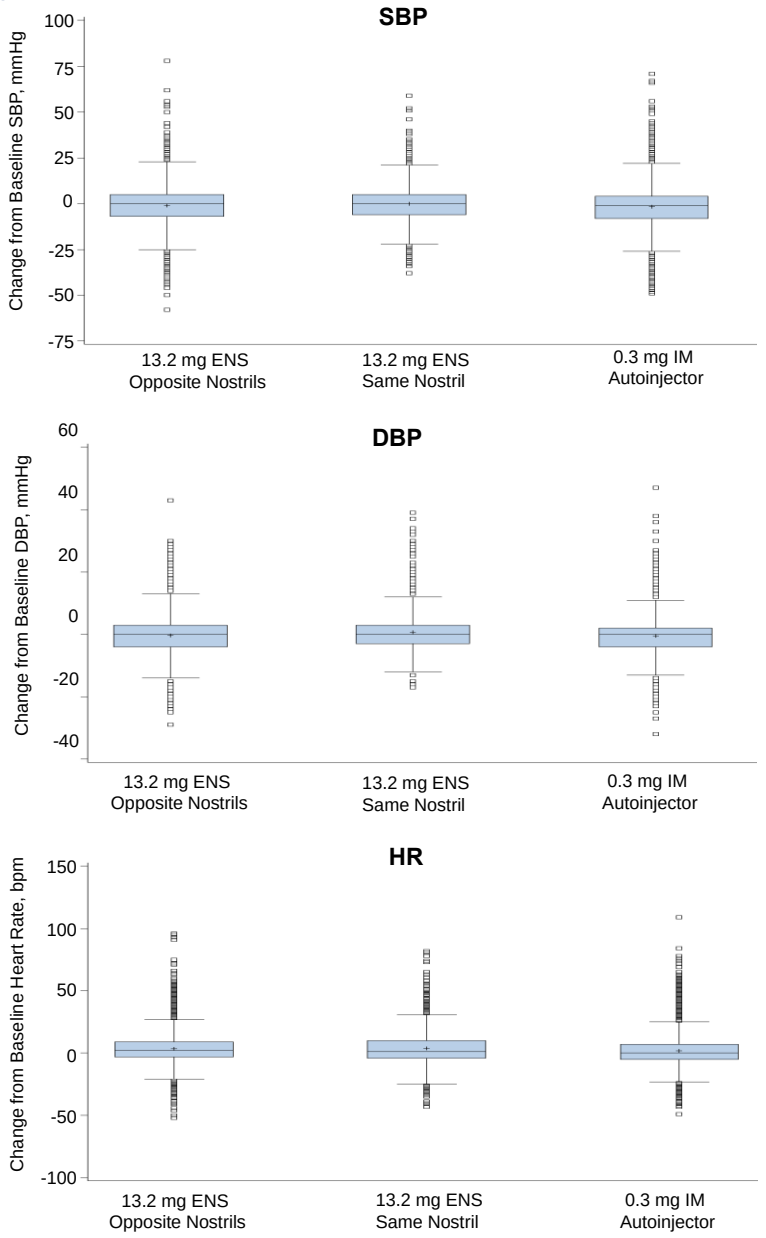


Figure 2. Median baseline-adjusted plasma epinephrine concentration – time profiles from 0-30 minutes



Greenhawt M et al PK data and Lieberman J et al PD data 2024

Figure 3. Overall mean and median values for all timepoints for change from baseline in SBP, DBP, and HR. Square symbols indicate any individual value outside the whisker values at any timepoint.



largest and smallest observed values within 1.5 x the interquartile range from the upper (Q3) and lower (Q1) quartiles.

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.

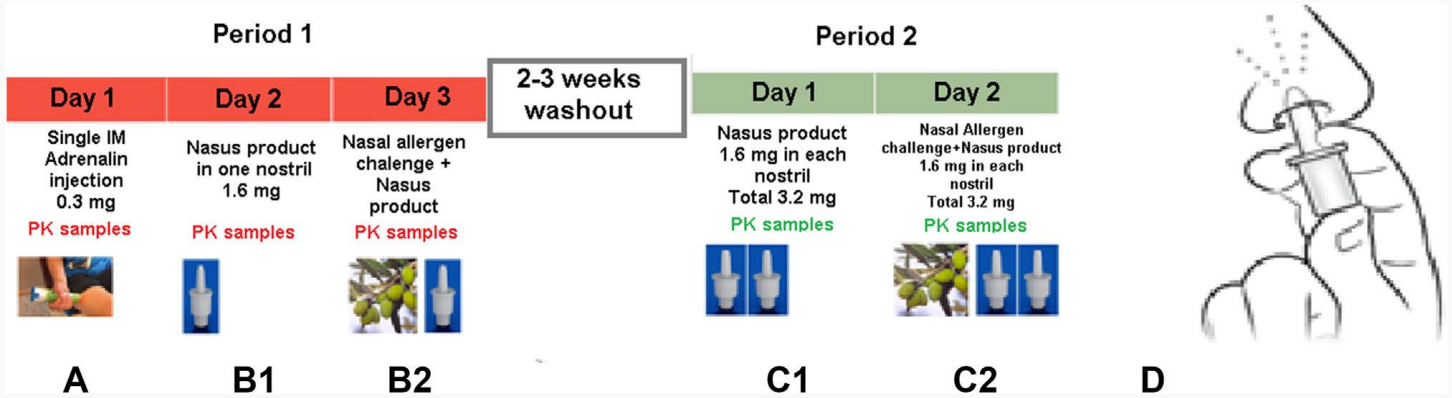


FIGURE 1. Study design consisting of 2 periods of epinephrine administration via intramuscular (IM) and intranasal (IN) routes. The 2 periods were separated by 2 to 3 weeks of washout. (**A**) On the first day of period 1, the subjects received a single IM injection of epinephrine (0.3 mg). (**B**) On each of the subsequent 2 days (ie, day 2 and day 3), the subjects received 1.6 mg of IN epinephrine (FMXIN002) in one nostril without (day 2, B1) or after a nasal allergen challenge (day 3, B2). (**C**) During period 2, the subjects received 1.6 mg of IN epinephrine (FMXIN002) in each nostril (total 3.2 mg) either without (day 1, C1) or after a nasal allergen challenge (day 2, C2). (**D**) An illustration of FMXIN002 nasal administration. *PK*, Pharmacokinetics.

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.

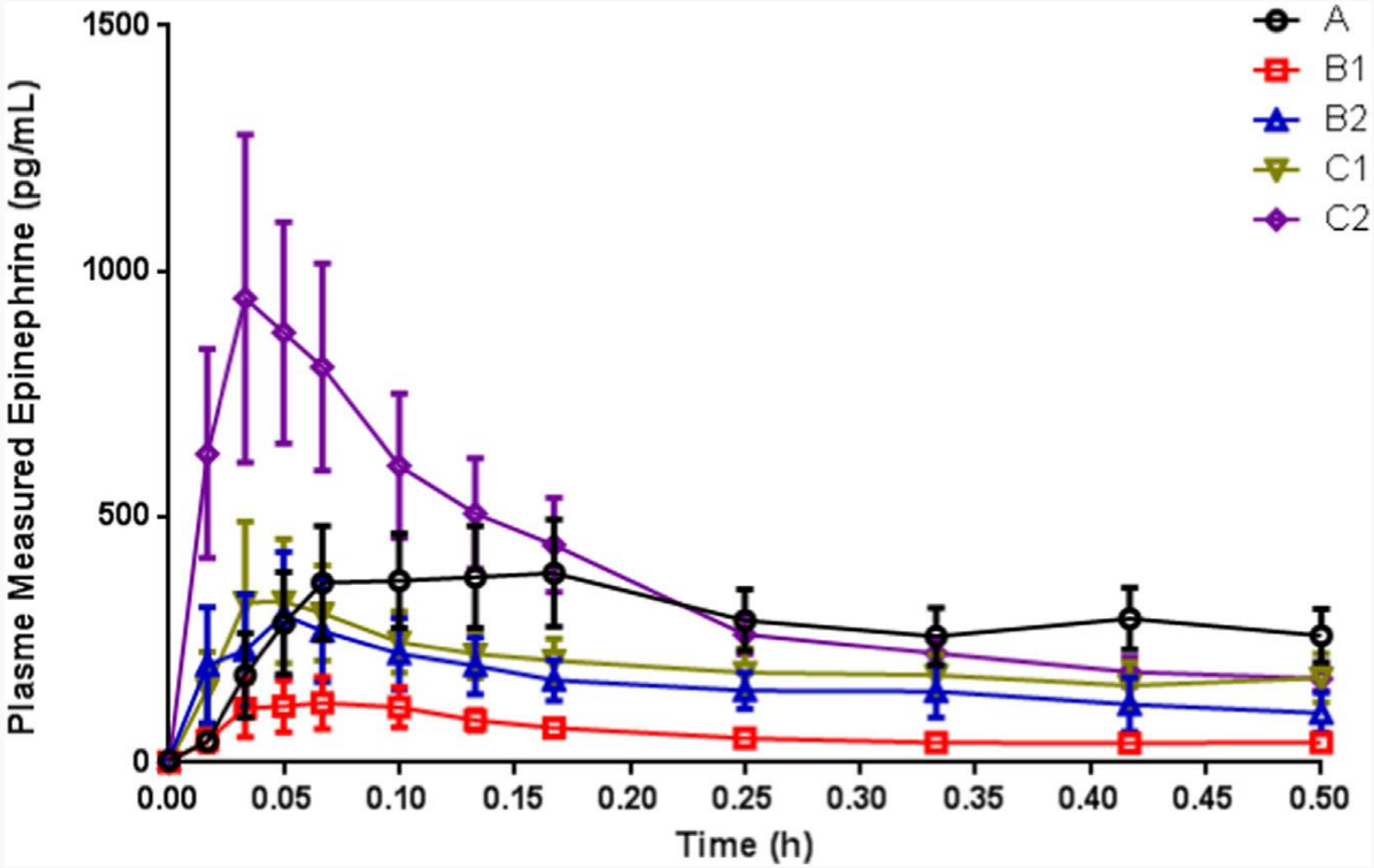


FIGURE 2. Mean plasma baseline-corrected epinephrine concentration-time profile at 30 minutes after dosing: linear scale. Results are mean + standard error.

Sublingual Epinephrine

Like IN epi, sublingual epi allows medications to bypass first pass metabolism of the liver, often making them faster than the oral route.

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

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

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

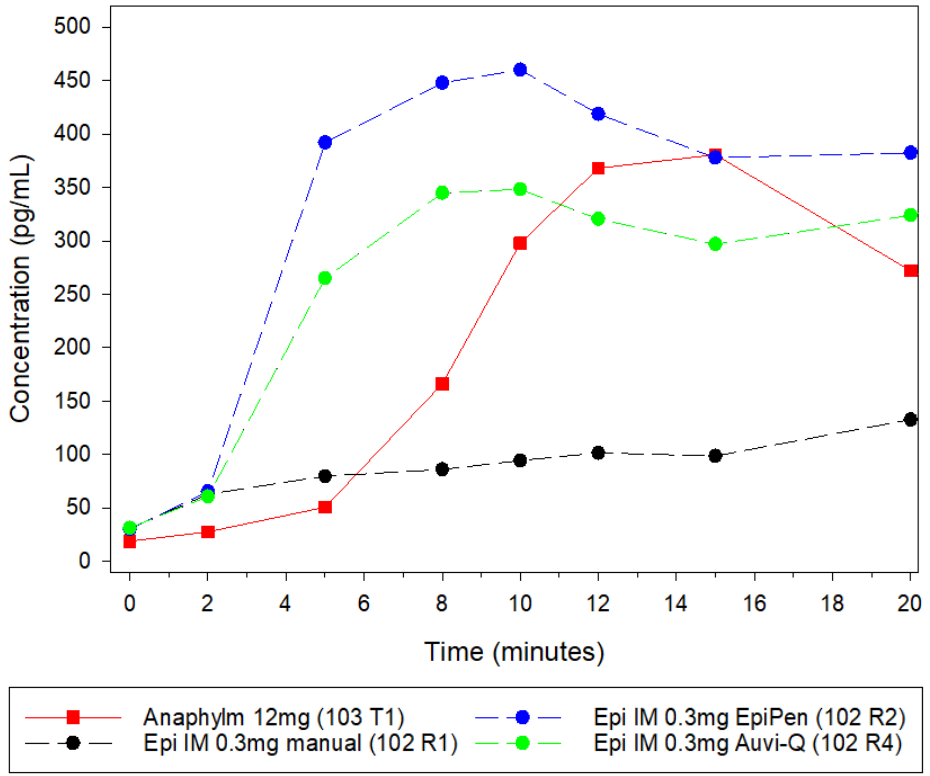


Table 1: Epinephrine PK Parameters by Treatment

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)
$AUC_{0\text{-}10}$, h·pg/mL	13.9	43.5	26.5	5.3
$AUC_{0\text{-}20}$, h·pg/mL	66.1	105.7	72.0	16.1
$AUC_{0\text{-}30}$, h·pg/mL	96.4	176.6	136.8	38.0
$AUC_{0\text{-}45}$, 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 (%).

Golden D, et al AAAAI 2024

Figure 2: Median Change from Baseline in Systolic Blood Pressure

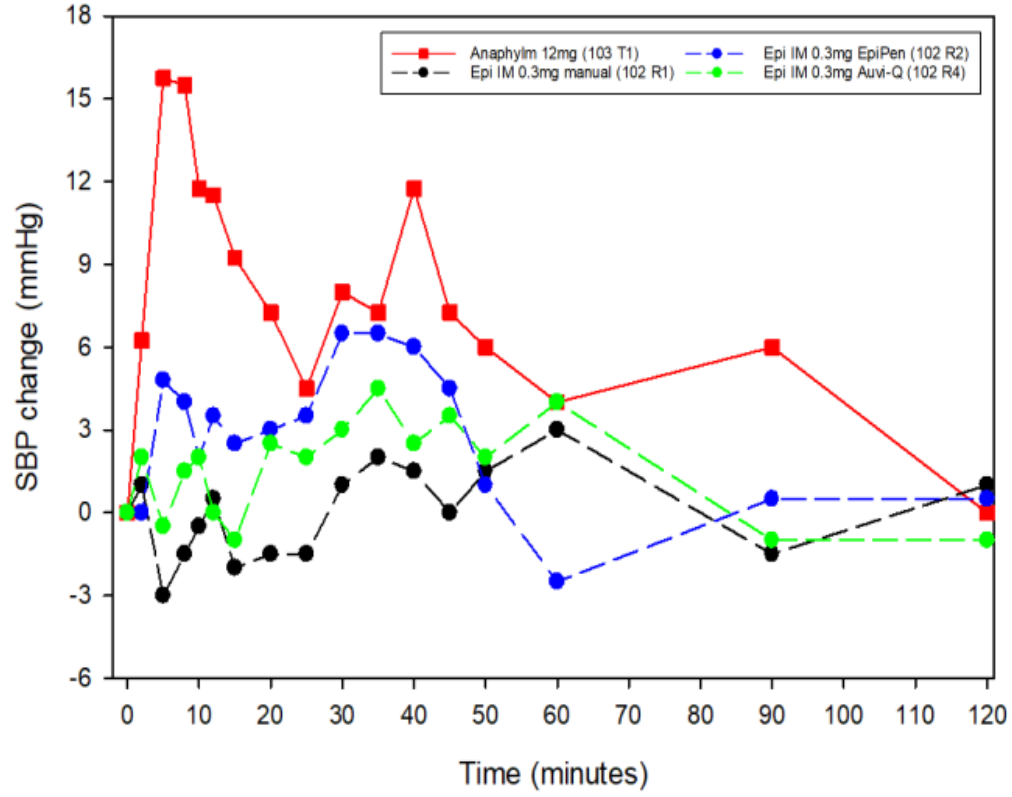
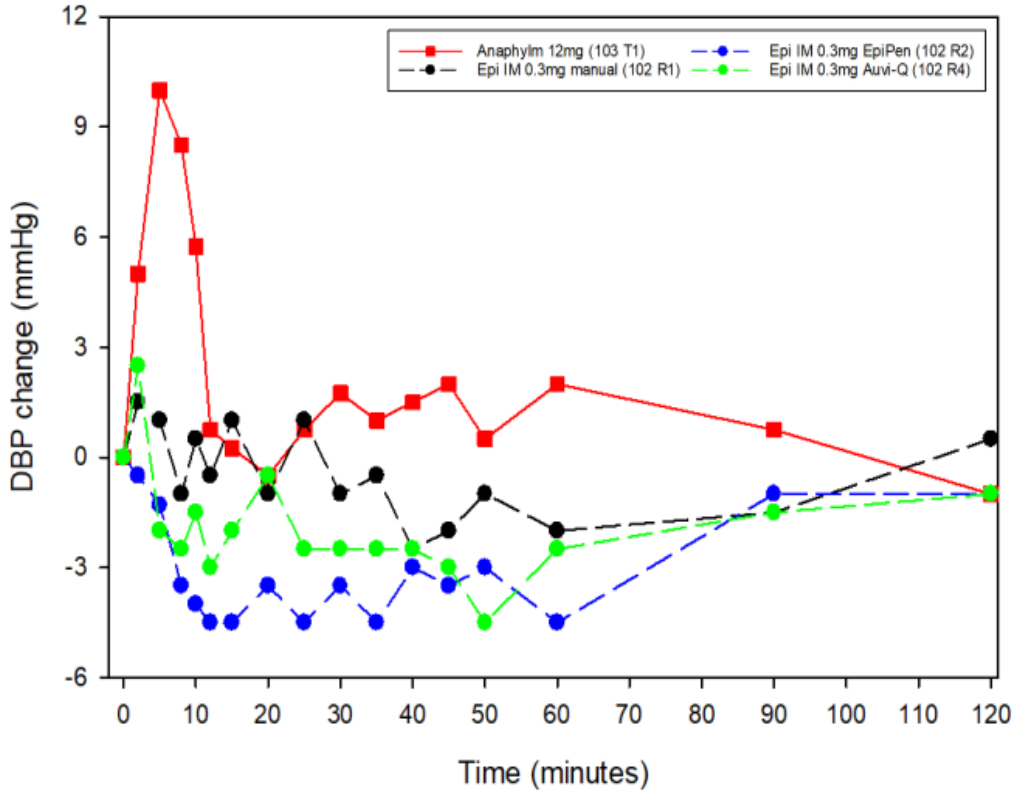


Figure 3: Median Change from Baseline in Diastolic Blood Pressure



Golden D, et al AAAAI 2024

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.