Risk-benefit assessment of *neffy*

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Ideal Properties of an Epinephrine Delivery Product

Does it work?

- Consistent and reproducible PK/PD profiles (no to minimal outliers) and drug administration that is not affected by anaphylaxis symptoms or pre-existing conditions or co-morbidities
- Robust and rapid PD effects that are especially important for severe anaphylaxis

Is it safe?

- No risk of injury and minimal side effects
- Minimize risk of overdosing with epinephrine
- Avoid side effects that are also anaphylaxis symptoms

Will patients use it?

- Minimal side effects
- Palatable
- Small
- Easy to use

Severe or Fatal Anaphylaxis Due to Laryngeal / Airway Edema in Children; Presence of Hypotension in Adults

Both

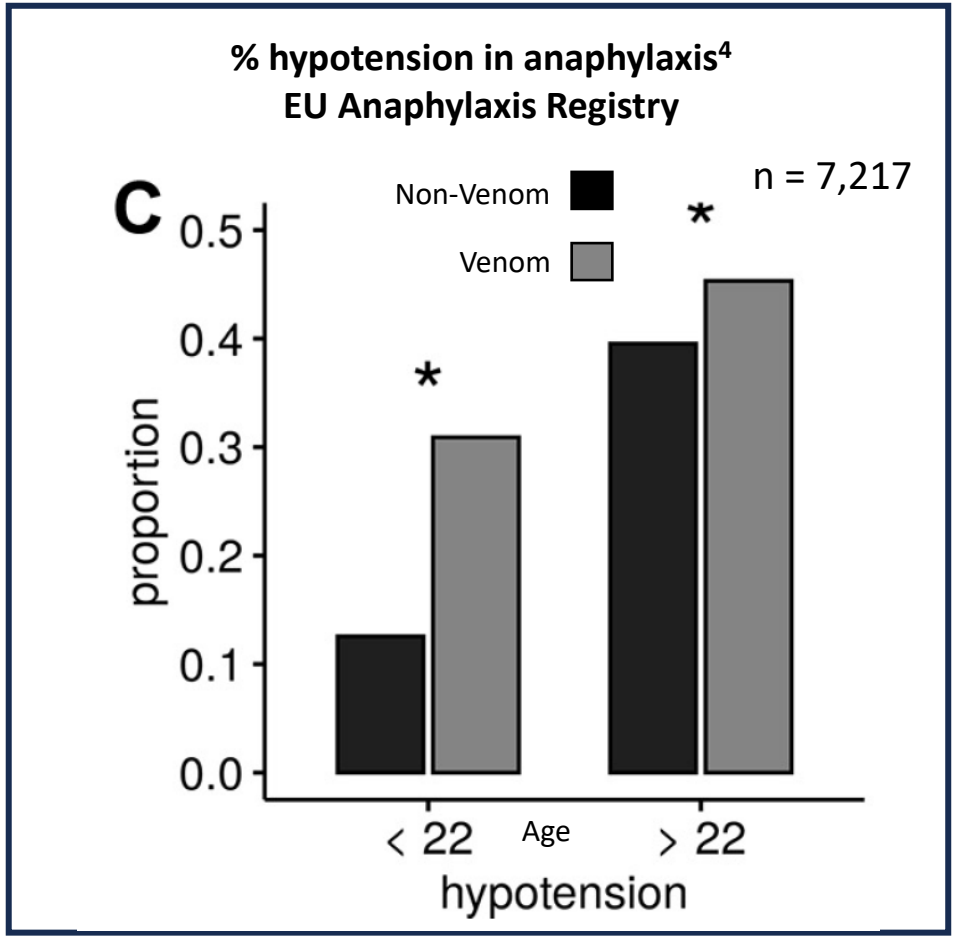
- Most frequent symptom is laryngeal edema: 41% to 46% prevalence of upper air way edema (lips to larynx) in fatal anaphylaxis[1, 2]

Children

- Deaths are rather secondary to the laryngeal edema, observed in 40%-50% of cases.[3]
- Cardiovascular involvement is rare in infants, most often observed in adolescents, probably related to age-dependent physiological changes."[3]

Adults

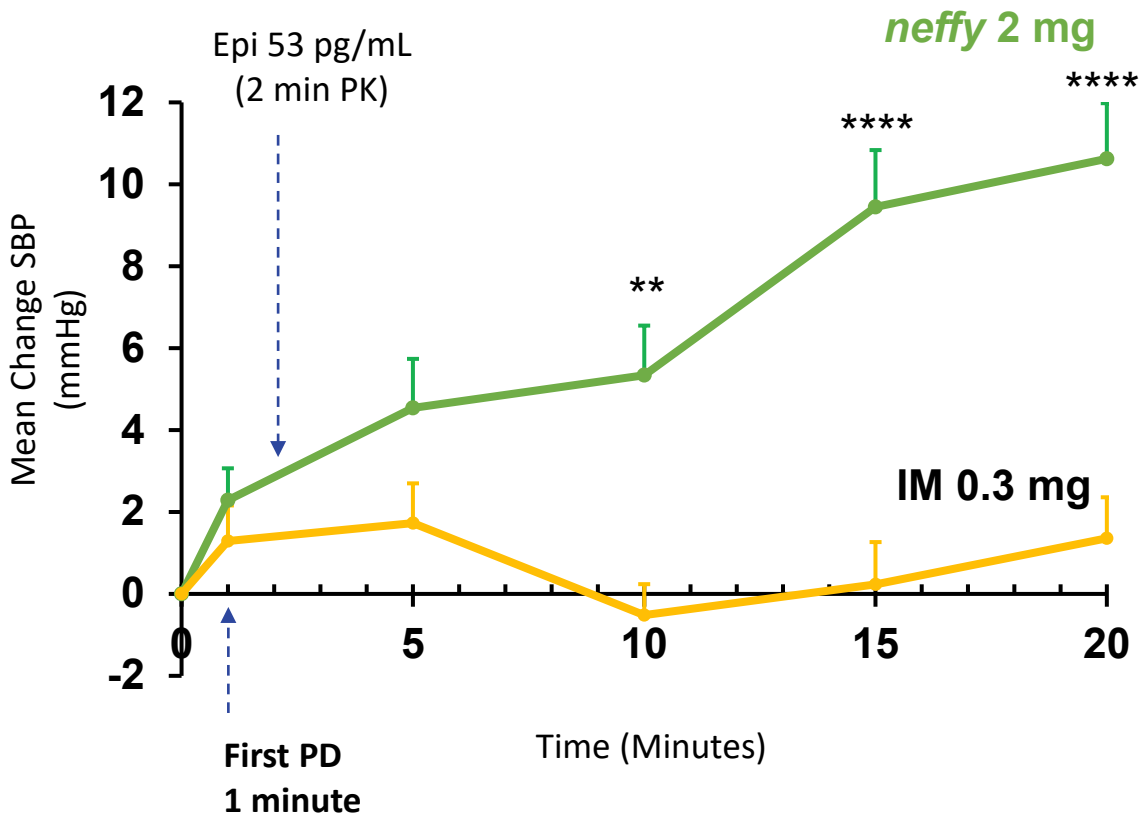
- Significantly higher rates of hypotension and cardiovascular involvement in older adults[4]



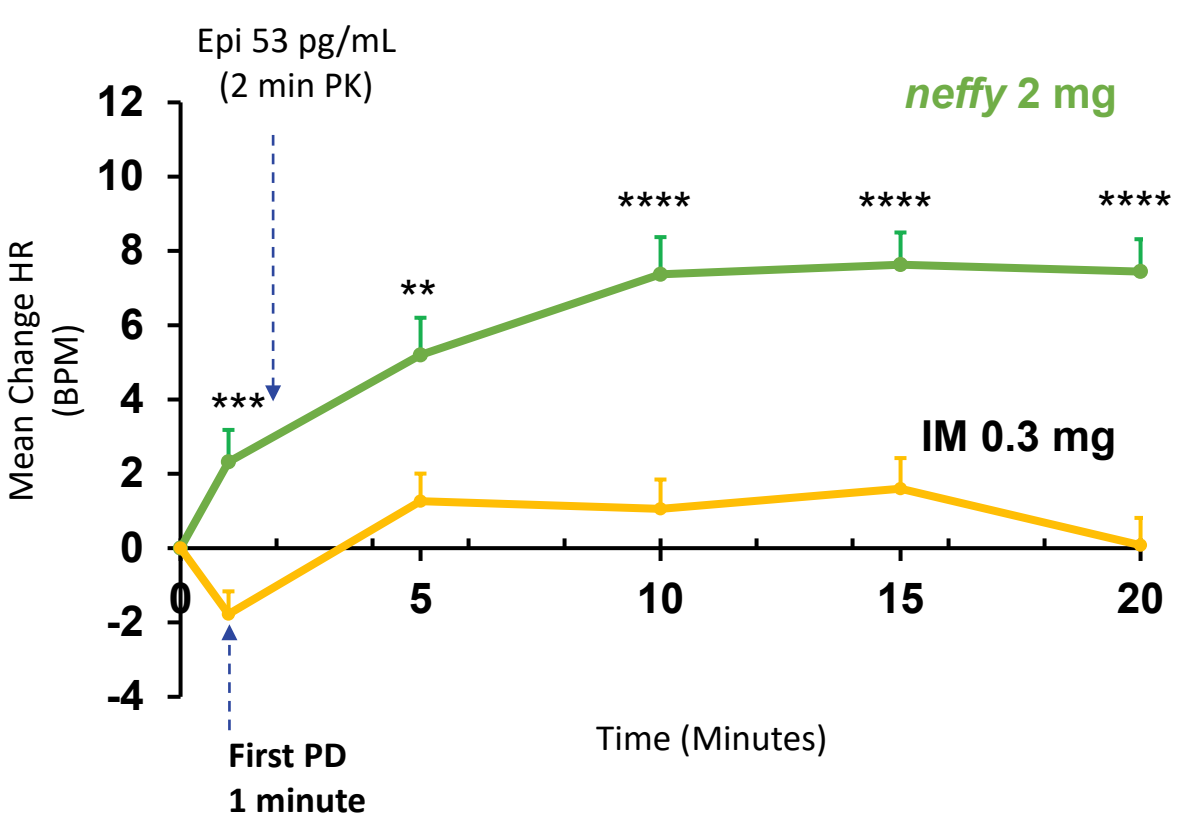
References: 1. Xu YS, et al. *Allergy Asthma Clin Immunol*. 2014. **2.** Pumphrey RS, et al. *J Clin Pathol*. 2000. **3.** Tanno LK, et al. *Pediatr Allergy Immunol*. 2020. **4.** Francuzik W et al. *J Allergy Clin Immunol*. 2021.

neffy Shows Rapid and Robust PD Response that Demonstrates Engagement of Receptors that Reverse Anaphylaxis Symptoms

Systolic Blood Pressure Response



Heart Rate Response

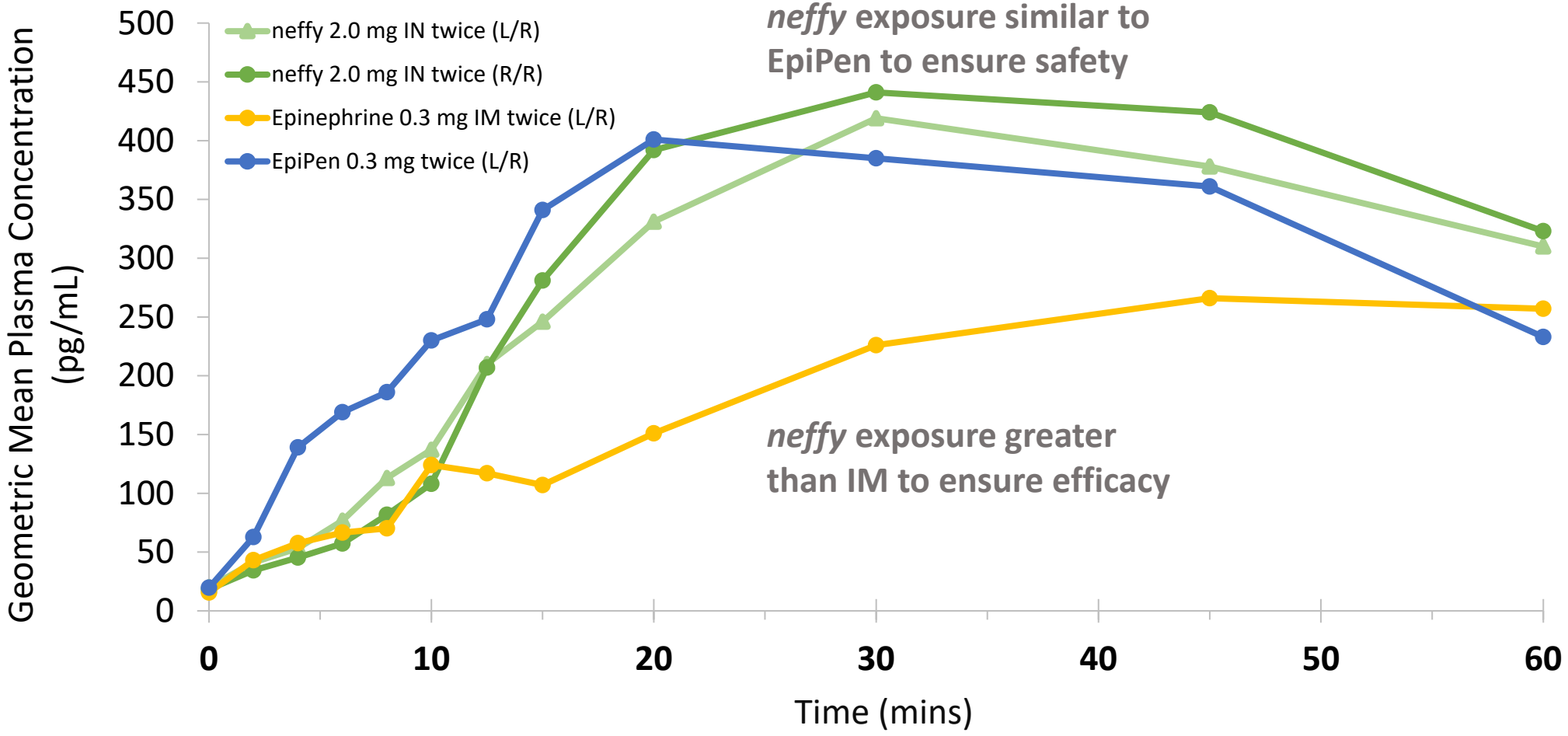


Significance level: ** p <0.01, *** p <0.001 **** p <0.0001

Integrated analysis of ARS clinical studies (EPI-15 and EPI-16)

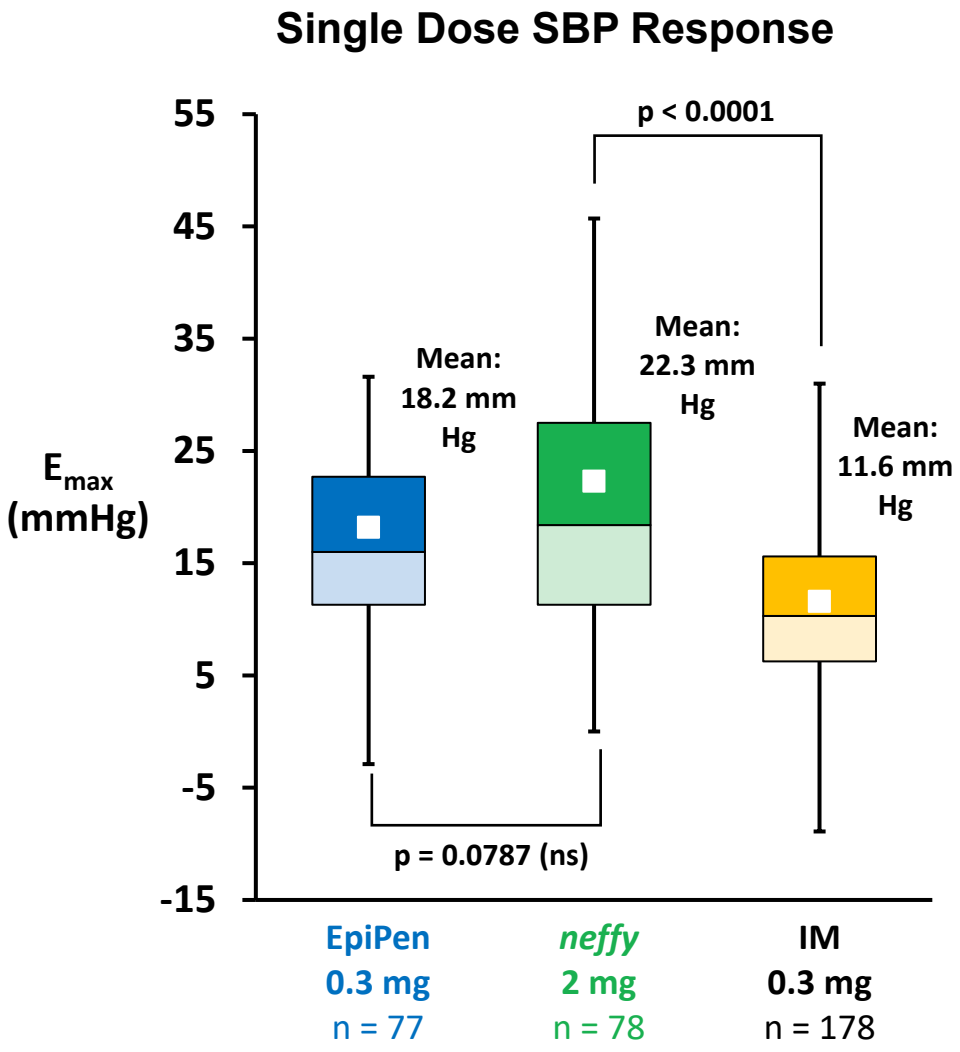
Exposures of Repeat Doses of *neffy* in Healthy Subjects are also in the Range of FDA Approved Epinephrine Injection Products

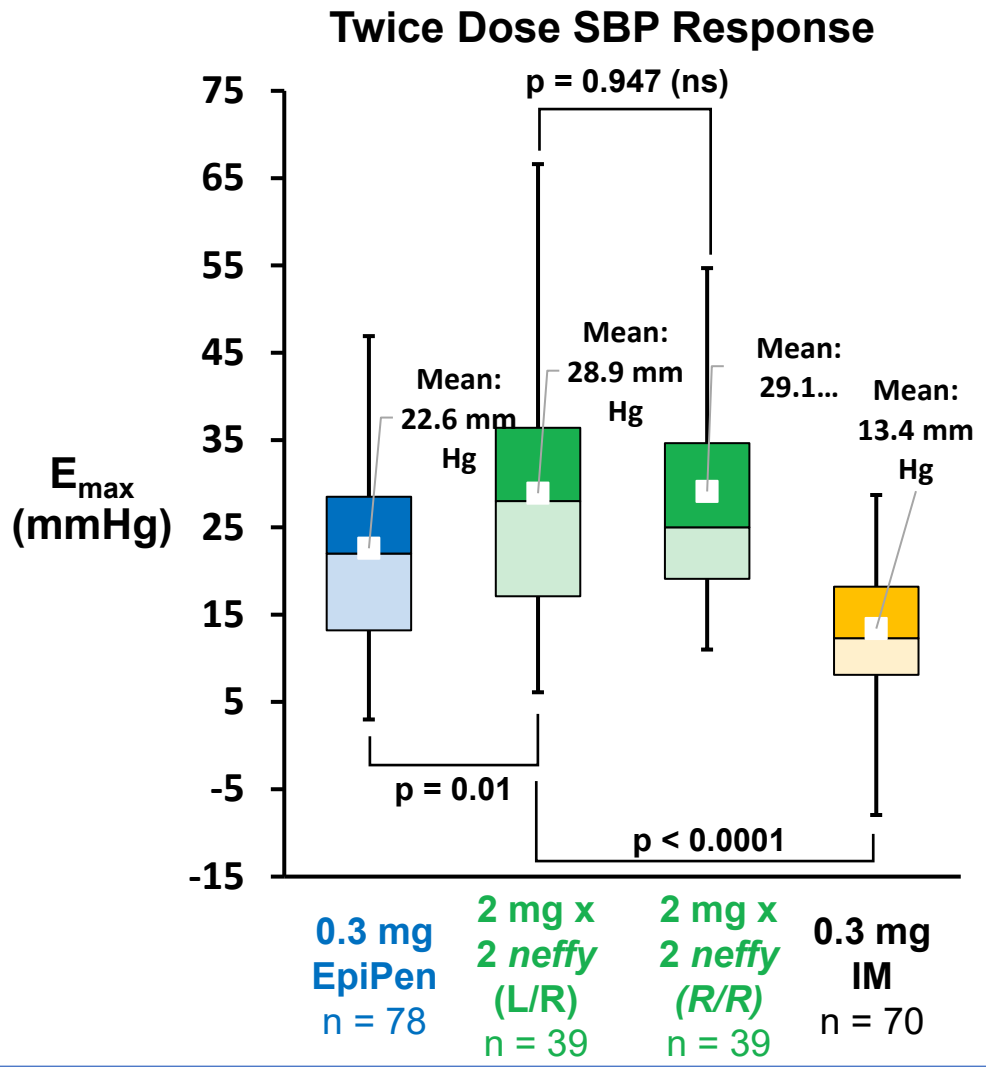
Repeat dosing 10 min apart in healthy subjects



Integrated data from ARS clinical studies, FDA Briefing Document May 2023 PADAC for NDA/BLA# 214697 (*neffy*)

PD Response as Shown to be at Least as Good as EpiPen, Supporting Engagement of Receptors that Reverse Anaphylaxis Symptoms





neffy Shows Robust and Rapid Clinical Resolution of Oral Food Challenge Induced Anaphylaxis Symptoms

Efficacy Study of *neffy* in Oral Food Challenge Induced Anaphylaxis (EPI-JP-03)[1]

Study Design: single arm, open-label study

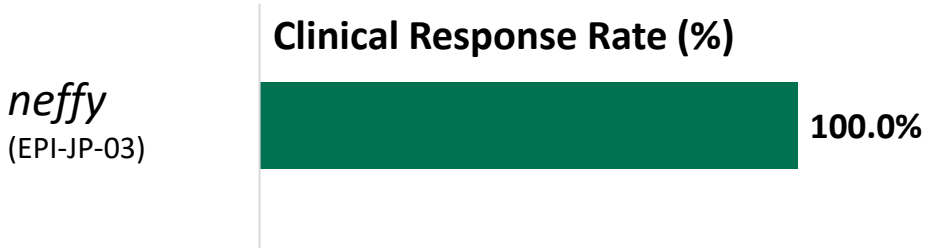
Participants: 15 pediatric subjects (aged 6 to 17):

- 9 subjects (30 kg+)
- 6 subjects (15-30 kg)

Patients experiencing Grade 2 (moderate) or higher anaphylaxis symptoms (out of 3 grade scale)[3] following oral food challenge dosed with a single dose of either 2 mg or 1 mg *neffy*:

- **Mucosal**: generalized urticaria/exanthema/wheal pruritus, swollen face, throat pain
- **GI**: moderate abdominal pain, recurrent emesis/diarrhea,
- **Respiratory**: repetitive cough, chest tightness/wheezing detectable via auscultation
- **Circulatory**: pale face/mild hypotension/tachycardia (>15 beats/min), light-headedness/feeling of "pending doom"/somnolence/headache

Study Outcomes



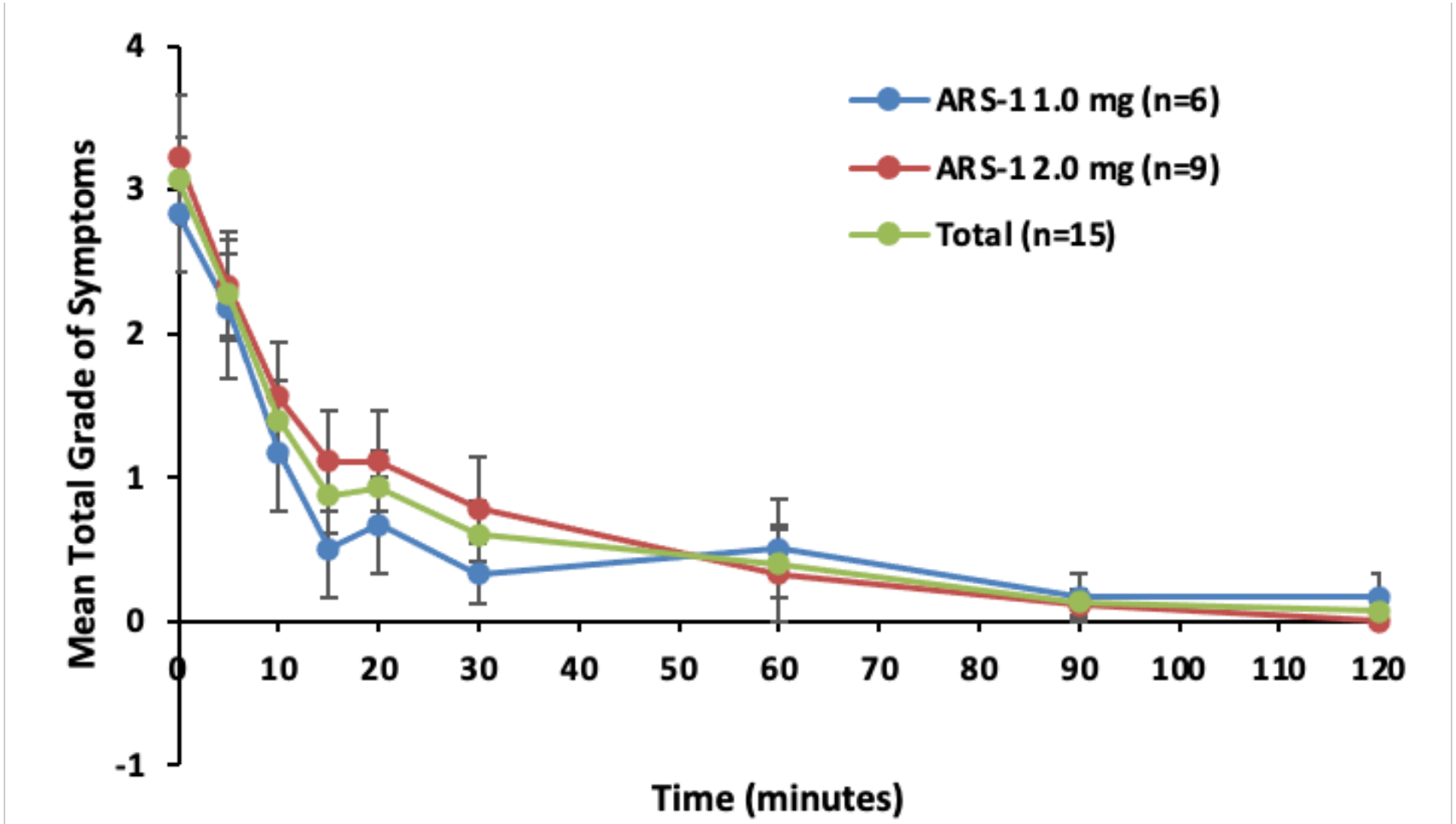
100% of patients responded to a single dose of *neffy* in the first 15 minutes, and did not require a second dose of epinephrine per treatment guidelines

100% of patients experienced complete resolution of the anaphylaxis symptoms with single dose of *neffy*[2]

16 min median time to complete resolution of anaphylaxis following single dose of *neffy*

References: 1. Ebisawa M, et al. Presentation at AAAAI 2024 (Washington DC). **2.** 100% of EPI-JP-03 patients dosed with *neffy* did not require a second dose in the first 15 minutes per guidelines because a response was not being observed, and 100% of patients achieved complete resolution of symptoms. 1 of the 16 subjects (6.7%) challenged with egg experienced a biphasic reaction 2h 45 min after being dosed with a single dose of *neffy* and achieving complete resolution of symptoms. This is consistent with the 12.8% frequency of biphasic reactions reported in children with food-induced anaphylaxis.(Gupta RS, et al. *J Allergy Clin Immunol Pract*. 2021).

neffy shows Robust and Rapid Clinical Resolution of Oral Food Challenge Induced Anaphylaxis Symptoms



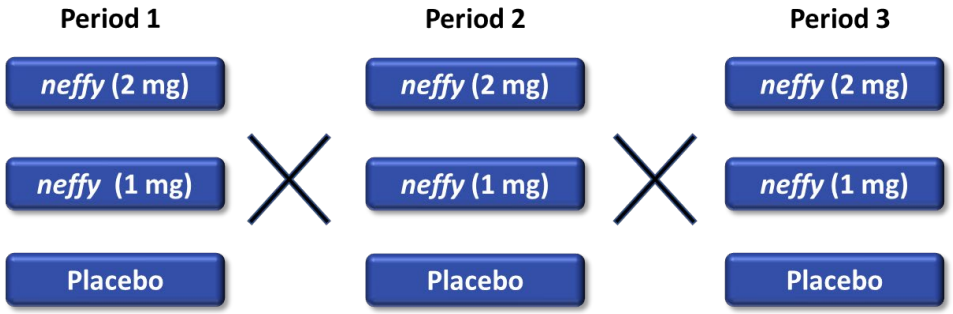
References: 1. Ebisawa M, et al. Presentation at AAAAI 2024 (Washington DC).

neffy Shows Robust and Rapid Clinical Responses in Treatment-Resistant Urticaria (Most Common Symptom of Anaphylaxis)

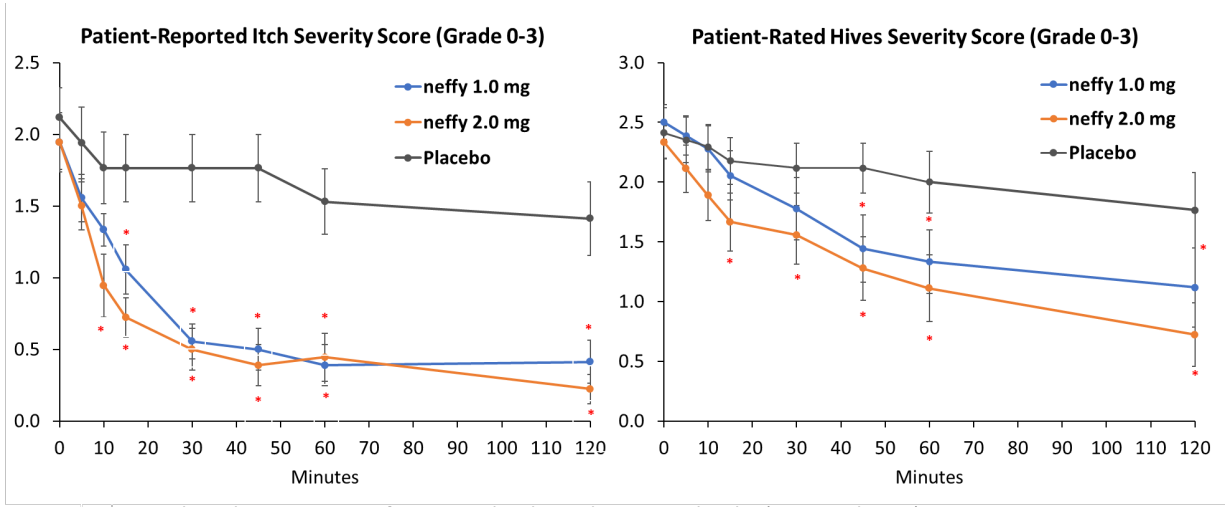
Randomized, Placebo-Controlled Efficacy Data in Treatment Refractory Chronic Urticaria (EPI-U01)[1]

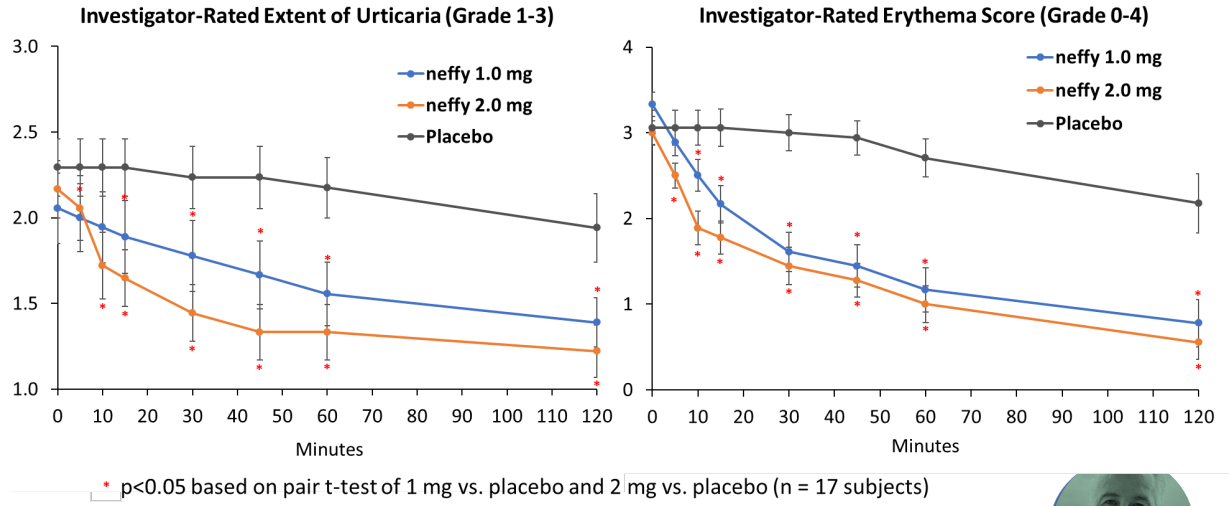
Study Design

randomized, placebo-controlled crossover trial study



- 18 chronic urticaria subjects who experience flares at least two times a week while on chronic treatment (antihistamines +/- Xolair)
- Patients come to clinic when experiencing a flare and are treated with 2 mg, 1 mg or placebo



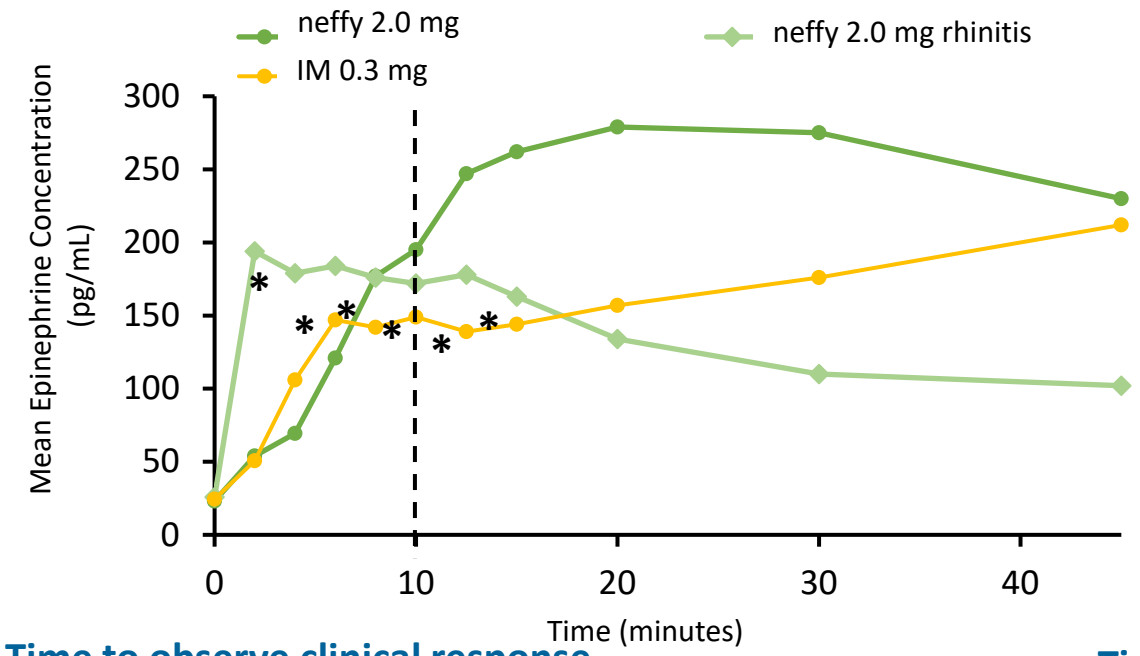


References: 1. Bernstein D, et al. Presentation at AAAAI 2024 (Washington DC).

Experimental NAC-Induced Rhinitis Does Not Negatively Impact *neffy*'s PK Profile (Allergic Rhinitis Subjects)

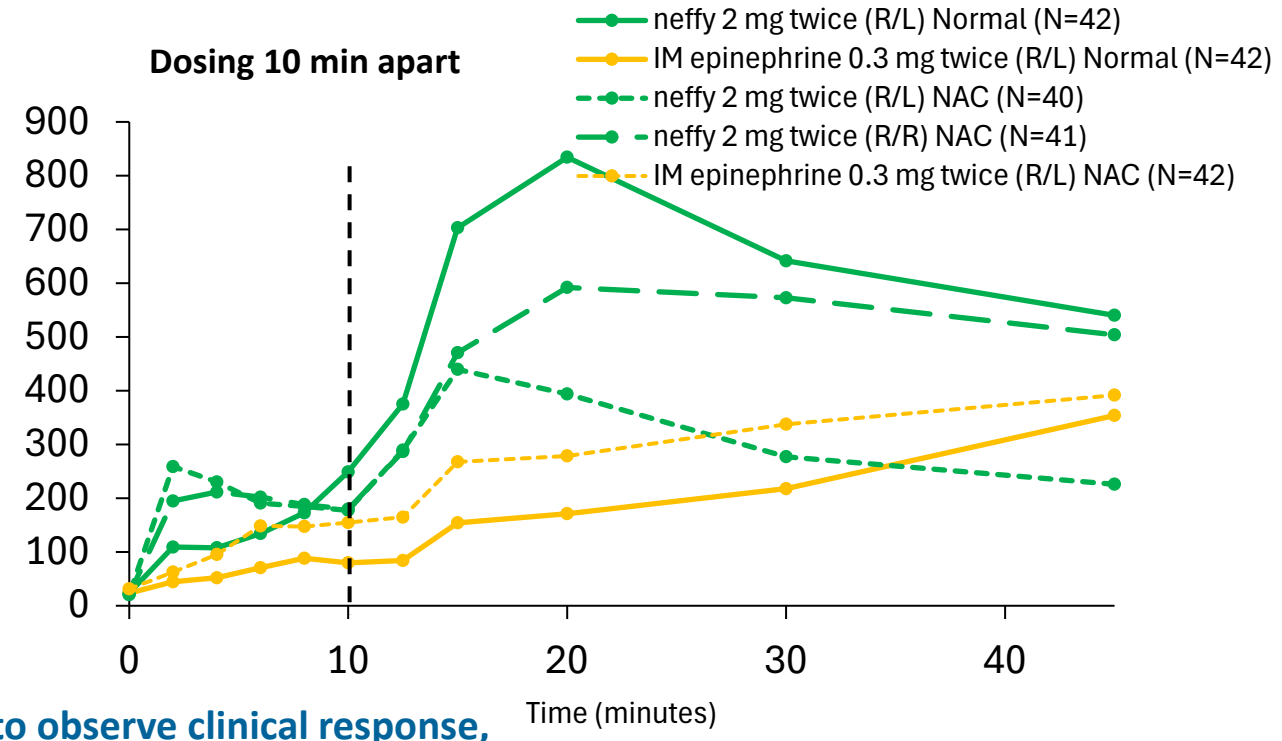
FDA Advisory Committee viewed *neffy* NAC data as "encouraging" and "favorable"

NAC-induced rhinitis accelerates absorption of single dose *neffy*, but within the range of injection



Time to observe clinical response, and re-dose per guidelines

Repeat dose under NAC-induced rhinitis supports similarity to injection for more severe cases of anaphylaxis

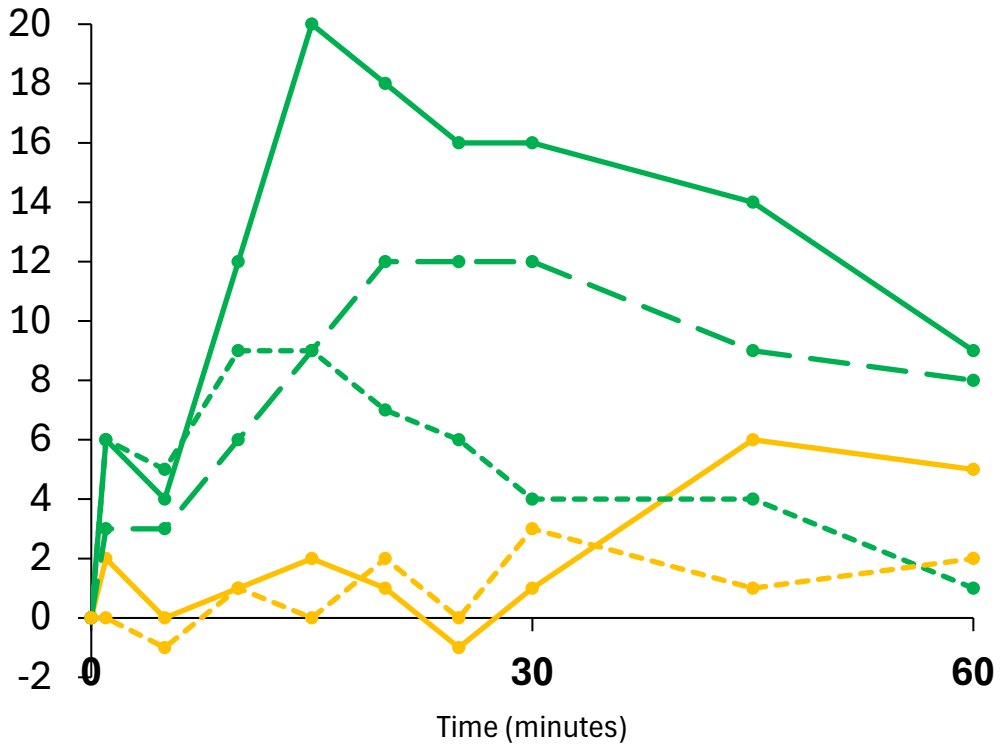


Time to observe clinical response, and re-dose per guidelines

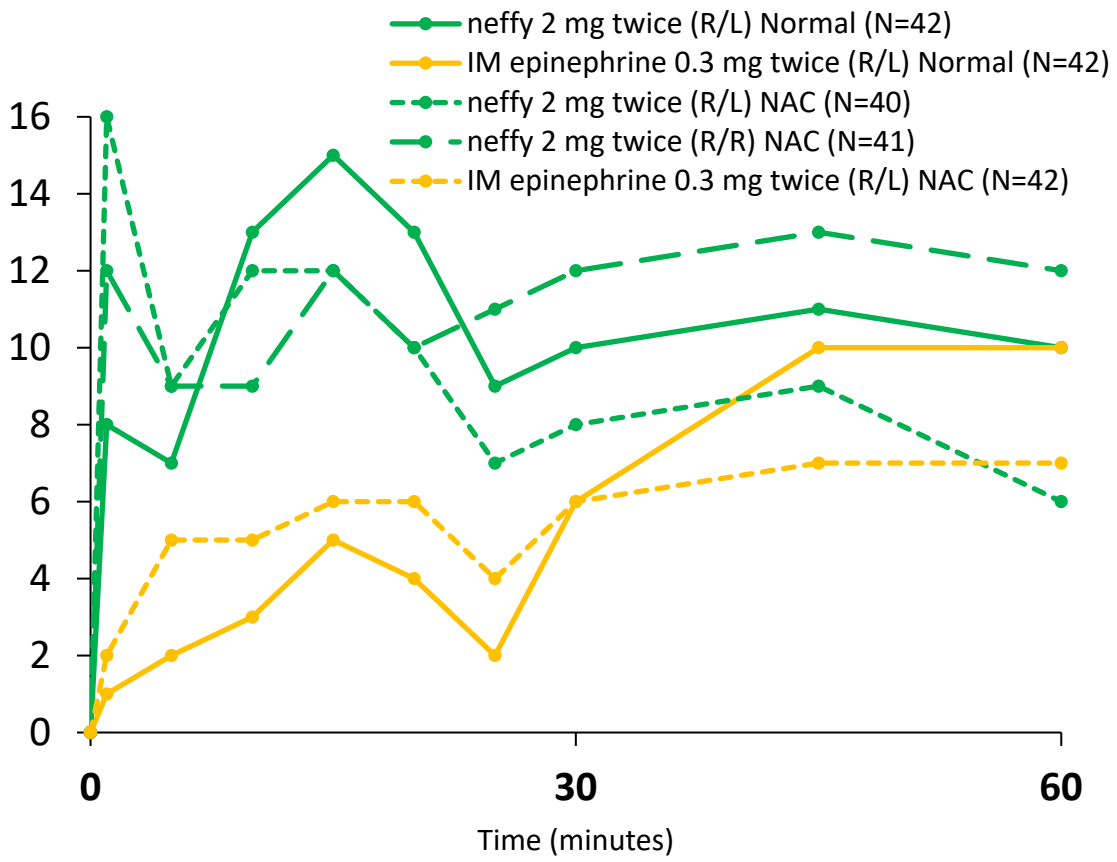
* Statistically significant differences between *neffy* with rhinitis compared to IM injection ($p < 0.05$)

Experimental NAC-Induced Rhinitis Does Not Negatively Impact *neffy*'s PD *P*rofile (Repeat Doses 10 min Apart)

Mean Change in Systolic Blood Pressure (mmHg)

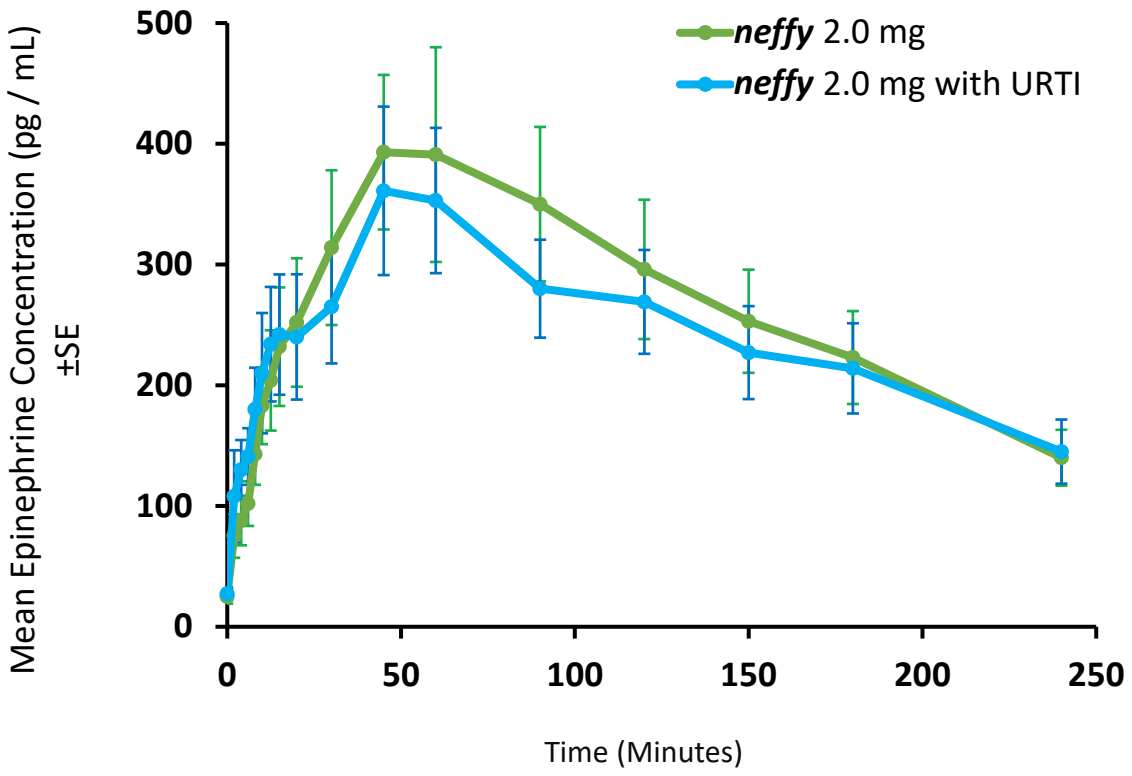


Mean Change in Heart Rate (bpm)

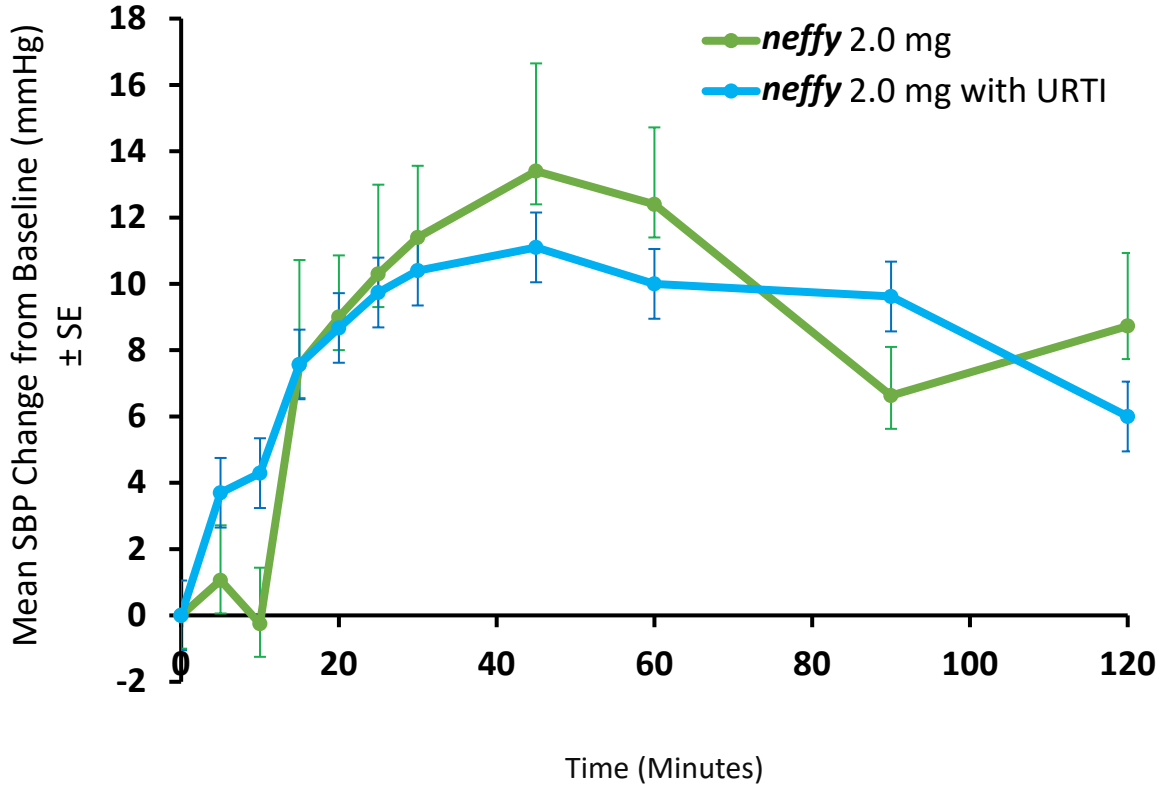


Upper Respiratory Tract Infection (URTI)-Induced Rhinitis has no Clinically Meaningful Impact on the PK/PD Profile of *neffy*

Mean Epinephrine Plasma

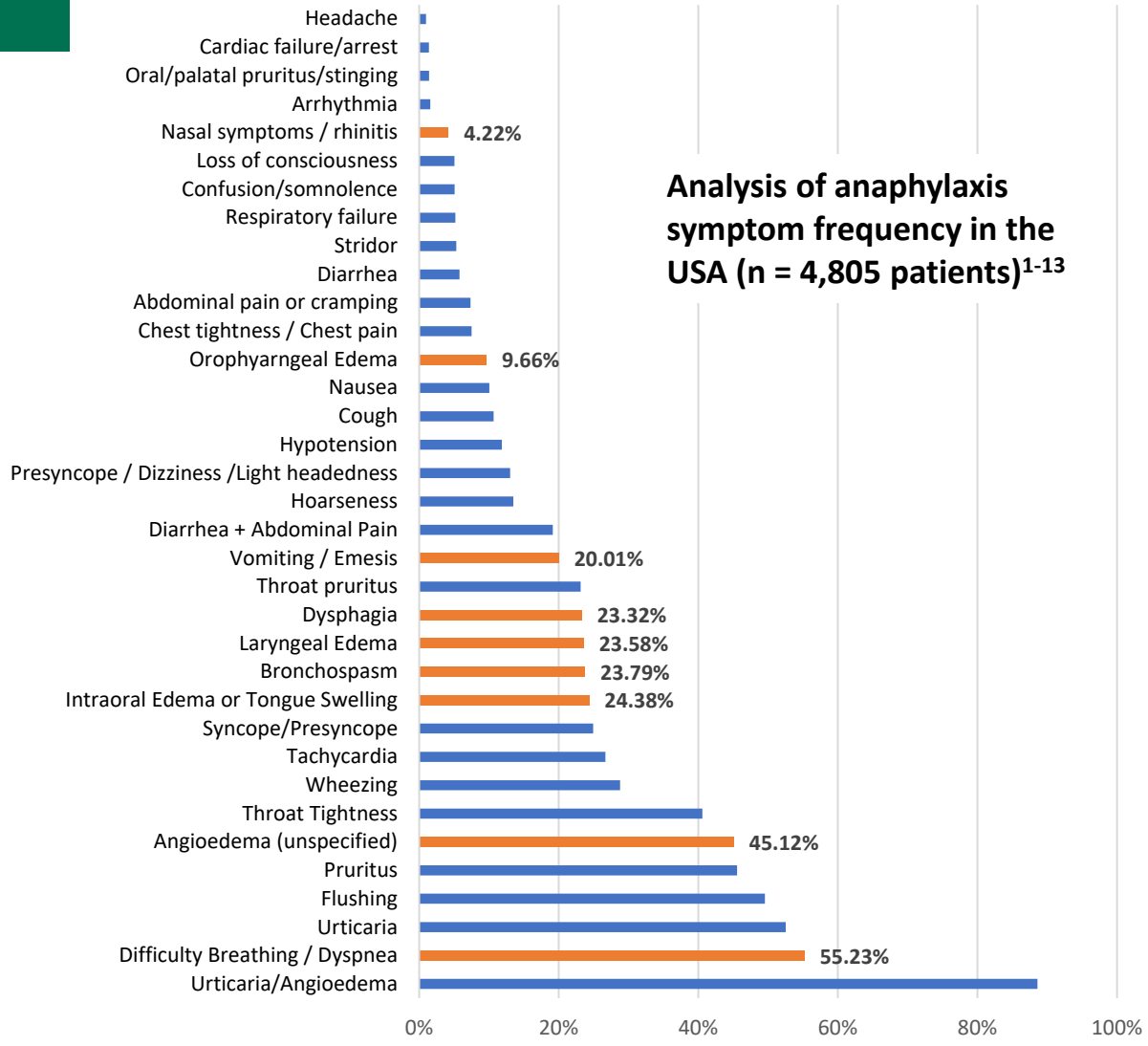


Mean Systolic Blood Pressure Change



N = 21 URTI / 16 Normal (returned)

PK/PD Profile and Ability to Dose May Be Influenced By Varying Conditions Including Anaphylaxis Itself



Analysis of anaphylaxis symptom frequency in the USA (n = 4,805 patients)[1-13]

Potential effect on <u>ability to dose or absorption profile</u> by theoretical route of administration for epinephrine

Anaphylaxis Symptom	US %	Intranasal	Sublingual	Oral*	Inhalation*
Nasal symptoms / rhinitis	4%	X			X
Oropharyngeal edema	10%		X	X	X
Vomiting / Emesis	20%		X	X	X
Dysphagia	23%			X	X
Laryngeal Edema	24%			X	X
Bronchospasm	24%				X
Intraoral Edema or Tongue Swelling	24%		X	X	X
Angioedema (e.g. face, lips, tongue or larynx)	45%		X	X	X
Difficulty Breathing / Dyspnea	55%				X

***insufficient oral and inhalation systemic absorption due to rapid conjugation and oxidation in GI tract or difficulty taking in enough puffs[14]**

References: 1. Pistiner M, et al. *J Allergy Clin Immunol Pract*. 2021. **2.** Jalil M, et al. Abstract at *AAAAI* 2020 Virtual Meeting. **3.** Gonzelez-Estrada A, et al. *Ann Allergy Asthma Immunol*. 2018. **4.** Lee S, et al. *J Allergy Clin Immunol*. 2017. **5.** Lee S, et al. *J Allergy Clin Immunol Pract.* 2014. **6.** Manivannan V, et al. *Am J Emerg Med.* 2014. **7.** Wood RA, et al. *J Allergy Clin Immunol* 2014. **8.** Walsh KE, et al. *Pharmacoepidemiol Drug Saf* 2013. **9.** Decker WW, et al. *J Allergy Clin Immunol.* 2008. **10.** Ross MP, et al. *J Allergy Clin Immunol*. 2008. **11.** Webb LM & Lieberman P. *Ann Allergy Asthma Immunol.* 2006. **12.** Ditto AM, et al. *Ann Allergy Asthma Immunol.* 1996. **13.** Rudders SA, et al. *Pediatrics*. 2010.**14.** Simons KJ, et al. *J Allergy Clin Immunol.* 2004. Note that some publications do not specify angioedema symptom subtype. Angioedema subtype frequency aggregated when reported.

Excellent Tolerability and Palatability

Adverse events generally mild in nature with no meaningful nasal irritation or pain up to 4 mg dose

No serious adverse events in any clinical study

No risk of needle-related injuries or blood vessel injections with *neffy*

Most common adverse events (>5%) were mild nasal discomfort (9.7%) and mild headache (6%), with no correlation of nasal discomfort to pain or irritation

- Mean VAS pain scores between 5 to 8 out of 100 (no stinging or burning)
- No irritation based on formal assessment (no erythema or ulcers)

Excellent palatability – no taste or smell with *neffy*

- "Inherent bitterness of epinephrine may hinder acceptability for patients, especially children"[1]

References: 1. Rachid O, et al. *AAPS PharmaSciTech.* 2010.

Adverse Event Profile Compares Favorably to Autoinjectors

Incidence of adverse events in *neffy,* EpiPen and Auvi-Q studies (greater than 5% frequency)

Adverse Event	2 mg neffy[1]	0.3 mg EpiPen[2]	0.3 mg Auvi-Q[2]
Injection-site erythema	0%	32.6%	31.3%
Injection-site pain	0%	24.4%	13.4%
Tremors	0%	14.1%	13.4%
Mild nasal discomfort	9.7%	0%	0%
Mild headache	6.0%	<5%	<5%
Anxiety	<1%	7.4%	10.4%
Injection-site bleeding	0%	9.6%	4.5%
Injection-site induration	0%	6.7%	4.5%

References: 1. FDA Advisory Committee, **2.** Edwards ES, et al. *Ann Allergy Asthma Immunol.* 2013.

Low Dose is an Important Benefit of *neffy* that Minimizes Risk of Overdosing, and Difficulty Monitoring Clinical Response

Epinephrine has a therapeutic window and potential for overdose

if too much is systemically absorbed too fast (e.g. IV bolus)[1, 2] – multiple cardiac events and fatalities reported in literature[3, 4]

2 mg *neffy* has essentially minimal risk of overexposure

even with higher bioavailability in the event of increased permeability during an allergic reaction or population variability (nasal abnormalities, impact of using other drugs or substances on nasal mucosa, etc.)

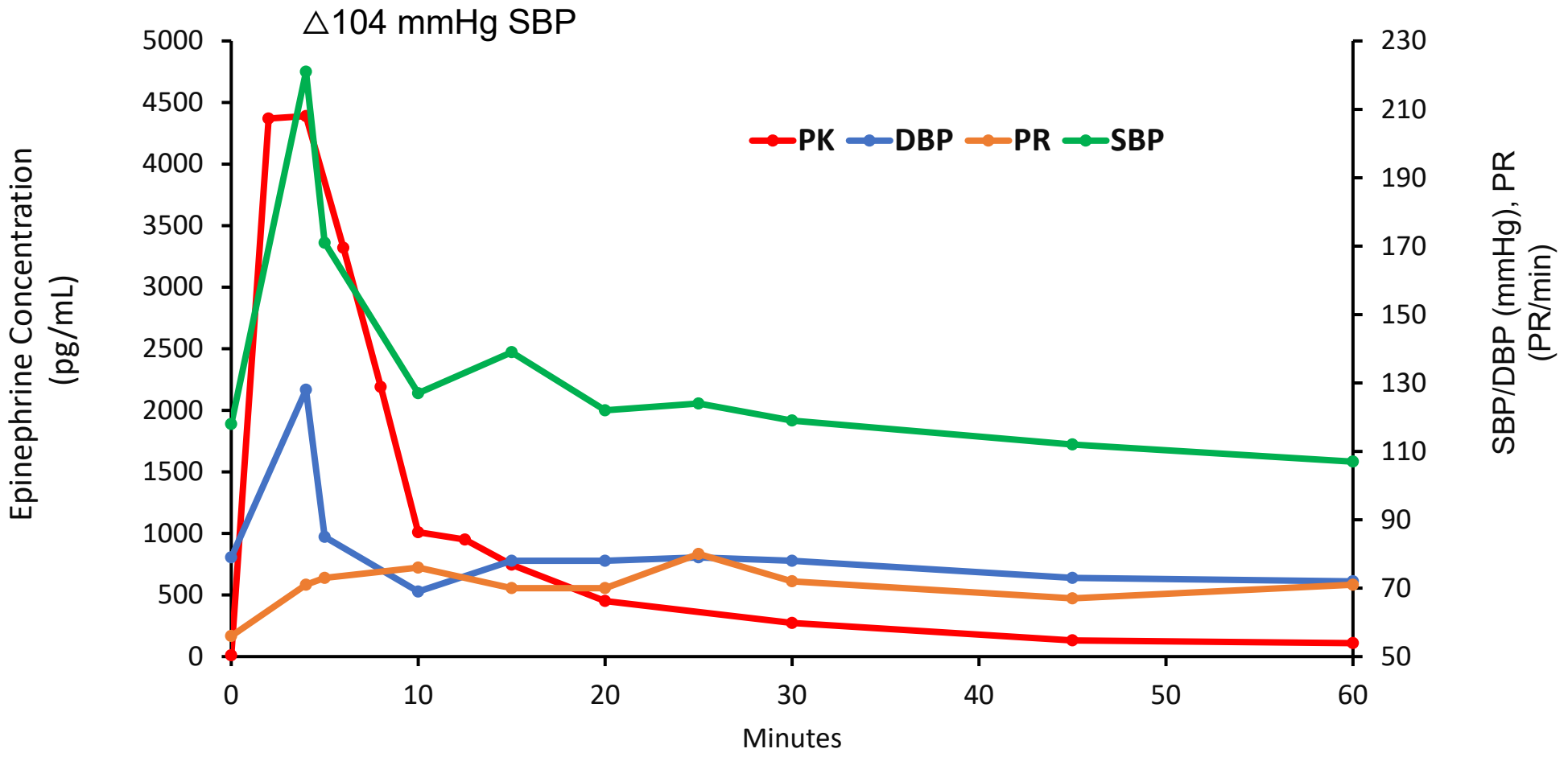
High dose of epinephrine can also lead to swallowing of non-absorbed epinephrine and GI side effects (vomiting/abdominal pain)[5, 6]

Vomiting/abdominal pain is a common symptom of food-induced anaphylaxis (especially biphasic) that can confound monitoring of clinical response leading to unnecessary treatment and re-dosing[7, 8, 9]

neffy has minimal to no GI side effects

References: 1. Casale TB, et al. *Ann Allergy Asthma Immunol.* 2024. **2.** Ebisawa M, et al. *J Allergy Clin Immunol Glob.* 2023. **3.** Pumphrey RS, et al. *Clin Exp Allergy*. 2020. **4.** Ring J, et al. *Dtsch Arztebl Int.* 2018. **5.** Schlegel C, et al. *J Dtsch Dermatol Ges*. 2009. **6.** Dworaczyk D & Hunt A. Presentation at AAAAI 2023 (San Antonio, Texas), **7.** Francuzik W et al. *J Allergy Clin Immunol*. 2021. **8.** Pflipsen MC & Colon KMV. *Am Fam Physician*. 2020. **9.** Gupta, RS, et al. *J Allergy Clin Immunol Pract*. 2021.

Too Much Epinephrine, too Fast, can be Dangerous, without More Benefit: Suspected IV Bolus Case-Study with EpiPen[1]



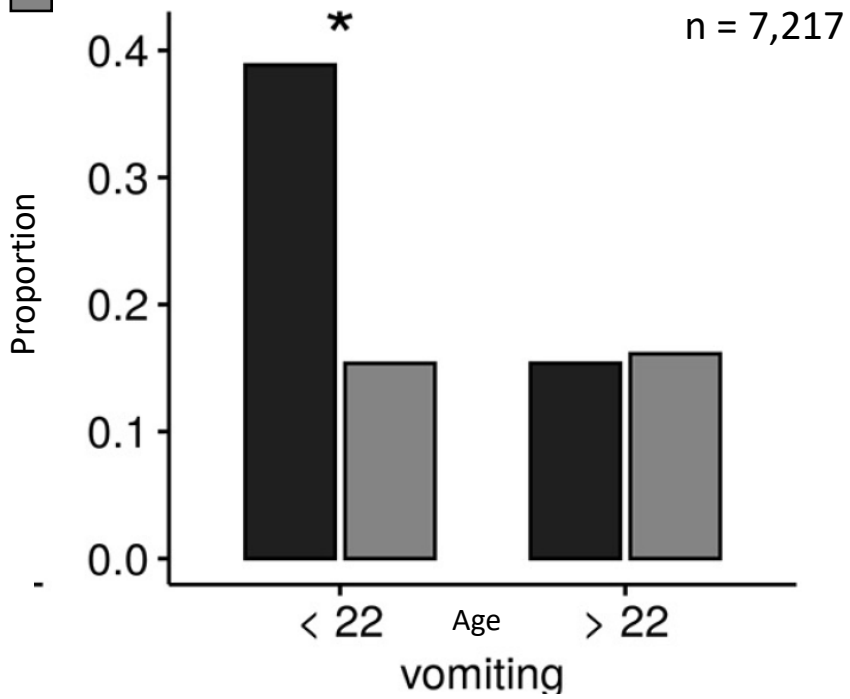
References: 1. Ebisawa, et al. *JACI: Global*, 2023.

Children more likely to experience vomiting and GI symptoms than adult anaphylaxis patients with non-venom allergies

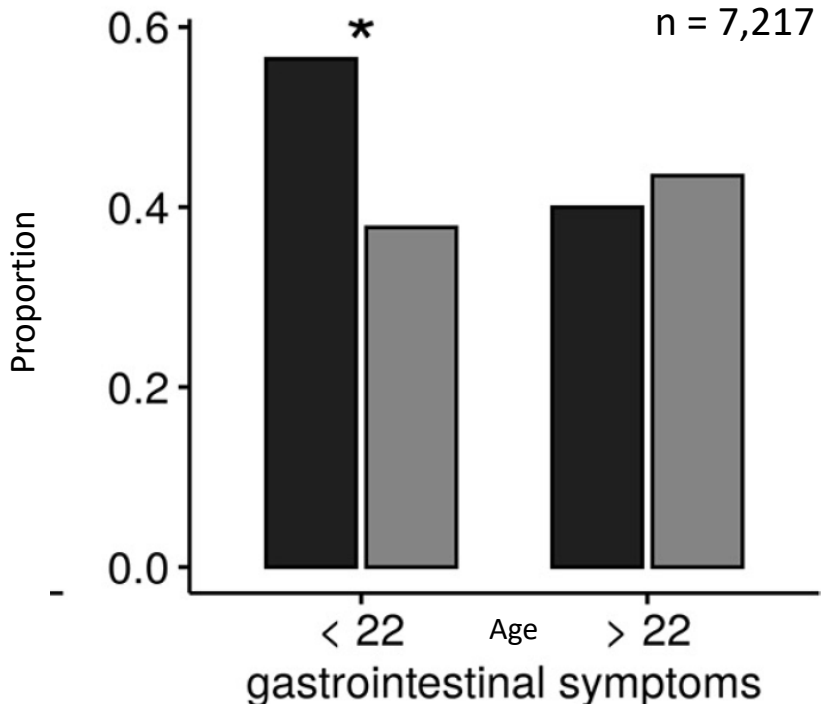
Non-Venom

Venom

~40% rate of pediatric vomiting in non-venom anaphylaxis



~60% rate of pediatric GI symptoms in non-venom anaphylaxis



Important side effect to avoid for monitoring of clinical outcomes
(and also a co-morbidity that could alter absorption of dosing via mouth)

References: 1. Francuzik W et al. *J Allergy Clin Immunol*. 2021.

Human Factors Studies and Real-World Data Have Proven that *neffy* is Easy for Patients to Carry and Simple to Administer

Proven ease of use in human factors studies and real-world emergency use settings

100% of adults (including passersby without allergies) able to use ***neffy*** successfully <u>without training</u>

100% of children (about half of the current autoinjector prescriptions) able to use ***neffy*** successfully <u>without training</u>

Same device available over the counter in NARCAN OTC (no training required)

Patients Should be Carrying and Dosing Sooner with *neffy*'s Potential Best-in-Class Epinephrine Product Profile

Does it work?

- PK/PD response shows onset within 1 minute after dosing
- Rapid efficacy profile in OFC anaphylaxis (100% response rate in first 15 min), as well as treatment-resistant urticaria
- Predictable dose-proportional PK/PD profile within range of approved injection products even under real-world co-morbidities (e.g. rhinitis)
- Only anaphylaxis symptom that may ***alter*** PK/dosing is rhinitis, and for *neffy*, no negative impact on PK/PD

Is it safe?

- Benign safety profile – mild nasal discomfort (9.7%) and mild headache (6%)
- No risk of injury (no needle) and minimal risk of overdose even with population variability (high bioavailability, low dose)
- No side effects (GI, vomiting, erythema) that could confound clinical monitoring and treatment

Will patients use it?

- Benign safety profile – mild nasal discomfort and headache
- Palatable – no meaningful pain/irritation, no taste/smell
- Small – fits in pocket
- Easy to use – 100% of adults and children can use without training (even passerby's); ability to dose not obstructed by anaphylaxis symptoms