NEEDLE – FREE ALTERNATIVE EPINEPHRINE NASAL SPRAY

for Type I Allergic Reactions

11 May 2023

ARS Pharmaceuticals, Inc.

Pulmonary-Allergy Drug Advisory Committee

Introduction

Richard Lowenthal, MSc, MSEL
CEO, President and Co-Founder
ARS Pharmaceuticals

neffy Designed to Address Current Unmet Medical Needs in Community

Significant unmet medical need	*neffy's design*
Fear of needles and self-injection	Needle-free
Complicated and difficult to carry devices	Easy to carry
Patients and caregivers reluctant to accept and use approved autoinjectors	Easy to use

neffy is a Saline Based Epinephrine Nasal Spray: Proven Triad of FDA-Approved Components

> 9 FDA approvals in allergy
(> 100 years of clinical experience)

2 FDA approvals
(> 1 million Rx)

TOSYMRA® VALTOCO®

6 FDA approvals
(> 55 million Rx)

NARCAN® VALTOCO® NAYZILAM®

TOSYMRA® IMITREX® ZAVZPRET®

neffy Designed for Easier Carriage

Indication and Dose

- **Proposed Indication**
  - Treatment of Type I allergic reactions, including anaphylaxis

- **Dose**
  - ***neffy* 2 mg** intranasal dose for adults and children ≥ 30 kg

Ongoing Development

- ***neffy* 1 mg** intranasal dose for children 15 kg to < 30 kg
- ***neffy* 1 mg** for treatment of urticaria
- ***neffy* 1 mg** for treatment of severe bronchospasm (asthma)

Development Program Centers on Pharmacology Studies

- Efficacy studies not ethical / feasible in severe Type I allergy patients
- ***neffy*** clinical studies developed in agreement with FDA to demonstrate
  - Bracketed pharmacokinetic (PK) exposures
  - Comparable pharmacodynamic (PD) responses
- > 1,100 administrations of neffy in > 600 subjects

Primary Studies	Patient Population
EPI 15	**Adult: Healthy volunteer (HCP administration)**
EPI 16	**Adult: Type 1 allergy patients (NAC induced rhinitis)**
EPI 17	**Adult: Type 1 allergy patients (self-administration): real-world study**
EPI 10	**Pediatric: Type 1 allergy patients: ≥ 30kg (NDA), 15 – < 30kg (planned)**

Considerations for Supporting *neffy* as a Needle-Free Alternative

- Significant unmet medical need
  - Needle-free route of administration could address barriers to epinephrine injection use
- PK and PD considerations
  - PK data from epinephrine injection products highly variable
  - ***neffy*** PK data bracketed between approved epinephrine products
  - ***neffy*** shows greater PD response vs IM injection
- ***neffy*** comparable to IM for patients under nasal challenge

Totality of Data Support Robust Pharmacologic Profile Comparable to Approved Injectable Epinephrine Products

PK bracketed by injection	**EPI 15** Healthy subjects (HCP administration)	**EPI 17** Type I allergy patients (self-administration)	**EPI 16** Allergic rhinitis patients (HCP administration)
Exposures ≥ IM/SC (efficacy) **Exposures < EpiPen (safety)** Prespecified: Cmax, Tmax, $pAUC_{0-20}$, $pAUC_{0-45}$	✓	✓	✓
Ad hoc: $pAUC_{0-10}$	✓ *Not statistically different*	✓	✓
PD comparable or better SBP, DBP and HR	✓	✓	✓

Additional Expert Responders

David Bernstein, MD
University of Cincinnati

Carlos Camargo, MD, DrPH
Massachusetts General Hospital

David Fleischer, MD
Children’s Hospital Colorado

Jay Lieberman, MD
The University of Tennessee Health Science Center

Phil Lieberman, MD
The University of Tennessee Health Science Center

Richard Lockey, MD
University of South Florida

Jonathan Spergel, MD, PhD
Children's Hospital of Philadelphia

Not Present
Special Recognition of Michael Kaliner, MD

Unmet Need in Use of Epinephrine

Dr. Thomas Casale, MD
Prof. of Medicine and Pediatrics
Director, Division of Allergy and Immunology Joy McCann Culverhouse Clinical Research Center
University of South Florida

Type I Allergic Reactions: Systemic Hypersensitivity Reactions With Increased Risk

- Caused by exposure to a **specific allergen**, most commonly **food**, **venom**, **drugs**
- **~35 to 45 million people in US** with more severe systemic Type I allergic reaction to allergens (e.g., 2+ organ systems involved)
- **Heavy disease burden on children and caregivers: ~42% are < 18 years; ~9% are ≥ 65 years**
- **Significant co-morbidities and symptomatic impact** on patient quality of life
- **More than half a million ER visits each year** due to systemic Type I allergic reactions[1]
- **Epinephrine is first-line treatment for severe type I allergic reactions**

1. Carrillo-Martin 2020

Basis of Approval for Community Use Products

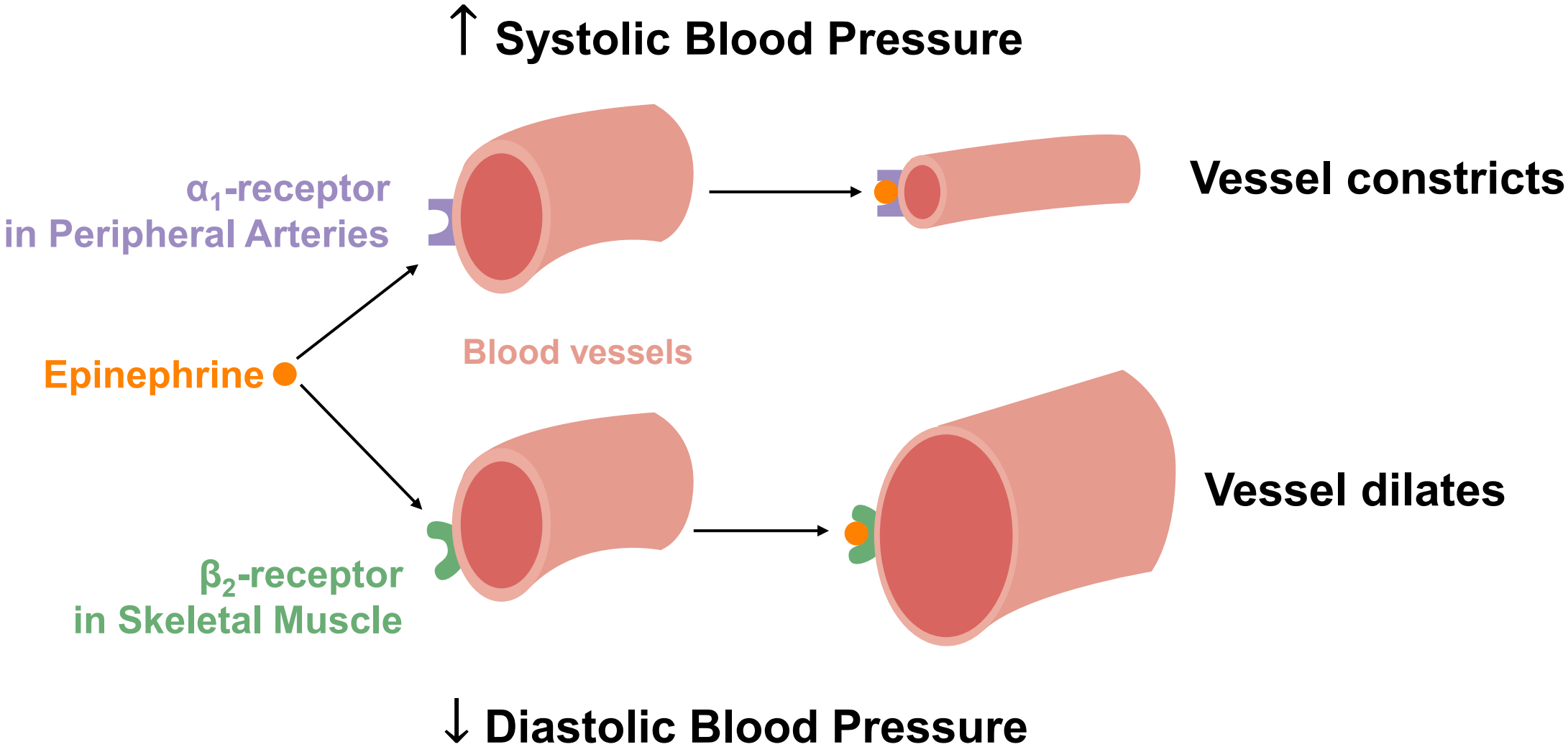
- Approved community use products include IM and SC dosing (FDA briefing book)
- Almost all approved without PK data

Device	Approval Basis	Pharmacokinetics (any data including literature)	FDA Approved Route and Dose
EpiPen® (1987)	No PK Data	Significant differences (EpiPen vs. IM) only known for ~10 yrs Blood vessel injection risk (IV bolus) known last 5 yrs	IM & SC 0.15 & 0.3 mg
Twinject® (2003)	No PK Data	No PK data known to date	IM & SC 0.15 & 0.3 mg
Adrenaclick® (2003)	No PK Data	No PK data known to date	IM & SC 0.15 & 0.3 mg
Auvi-Q® (2012)	Single PK Study	More rapid PK vs. IM, but slower PK vs. EpiPen (T_{max} = 20 min vs 10 min)	IM & SC 0.1, 0.15 & 0.3 mg
Symjepi® (2017)	No PK Data	ARS studies show slower PK vs ***neffy*** or other autoinjectors	IM & SC 0.15 & 0.3 mg
Teva EpiPen® (2018)	No PK Data	None to date; shorter needle and different activation force	IM & SC 0.15 & 0.3 mg

Epinephrine Used > 100 Years: Well Known Pharmacology and Mechanism of Action

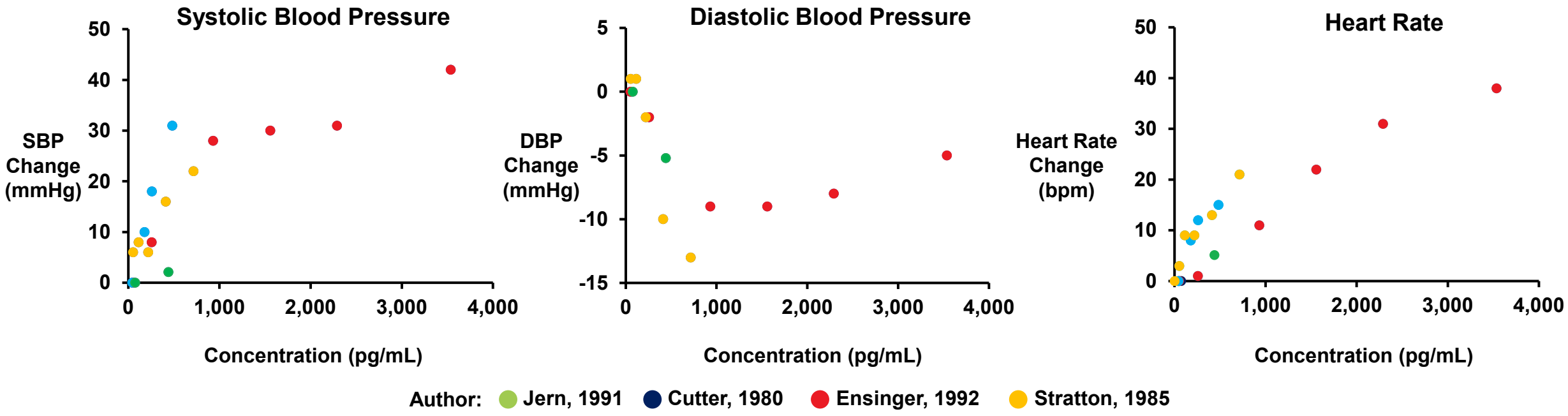
Adrenergic Receptor	Pharmacological Effect of Epinephrine	Clinical Effect of Epinephrine
α_1	• Increases systolic blood pressure • Causes blood vessel constriction • Decreases mucosal edema	• Relieves hypotension and shock • Relieves upper airway obstruction
β_1	• Increases blood pressure and heart rate	• Relieves hypotension and shock
β_2	• Relaxation of bronchial smooth muscles • Vasodilation in skeletal vasculature • Inhibits inflammatory mediator release from mast cells and basophils	• Increase in bronchial airflow • Increases blood flow to skeletal muscle • Reverses pathological histamine cascade

Epinephrine's Action on Vessels



Relevance of Pharmacodynamic Responses

- 2012 clinical pharmacology review for epinephrine injection, FDA concluded[1,2]
  - Positive correlation for epinephrine exposure with HR and SBP
  - Negative correlation for epinephrine exposure with DBP
    - Caused by β_2-mediated vasodilation in skeletal muscle



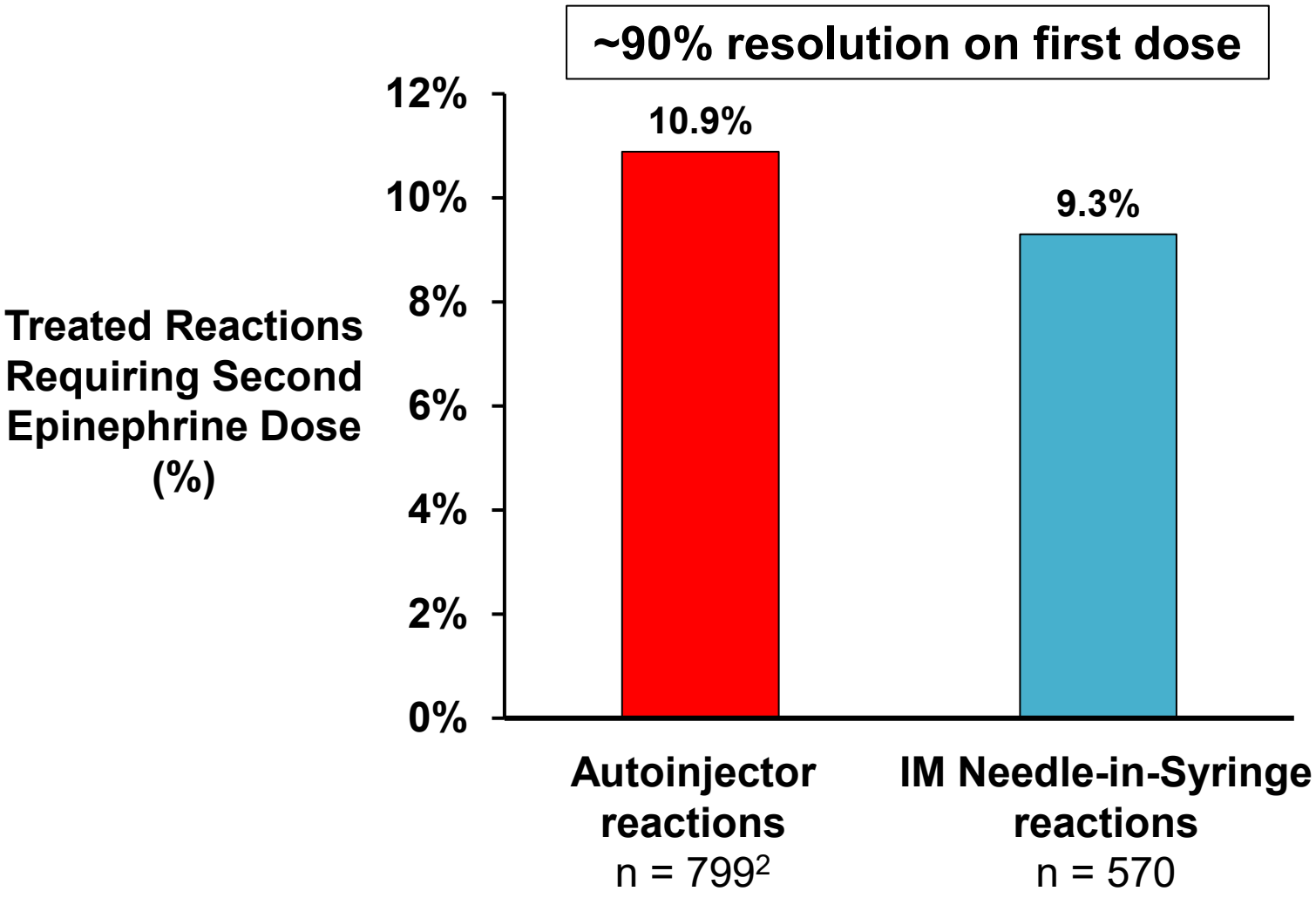
1. Worm 2020; Duvauchelle 2018, 2022; Clutter 1980; Stratton 1985 and Ensinger 1992; 2. NDA 205029

Route of Administration Should Not Impact Epinephrine Efficacy

- Available approved products include
  - Intramuscular (IM) or subcutaneous (SC) injection with needle and syringe
  - Autoinjectors (e.g., EpiPen) or prefilled syringe devices (e.g., Symjepi)
    - Per FDA labeling approved community use devices can be IM or SC depending on dosing technique and body mass
- Both real-world evidence and clinical data demonstrate same clinical outcomes between different devices
- Effect within 5 – 10 minutes with all injection products (IM needle and syringe, SC, or various autoinjectors)[1,2]

1. Brown 2004; 2. Dodd 2020

Second Dose Demonstrates Similar Effect Between IM and Autoinjectors



- Analysis of 12 studies with 100% autoinjector (≥ 80% EpiPen) or 100% IM-needle-and-syringe use in community or ED setting[1]
- Differences in PK profile across products do not impact efficacy based on need for repeat dosing to resolve symptoms

1. Patel 2021; 2. Kahveci 2020, Oya 2020, Kondo 2018, Cardona 2017, Oren 2007, De Swert 2008, Johnson 2014, Nogic 2016, Grabenhenrich 2018, Campbell 2015, Lee 2015, Shoshan 2013, Grabenhenrich 2018, Soller 2019, White 2015, Arkwright 2009, Gold 2000, Webb 2006, Noimark 2012, Kondo 2018, Cardona 2017

Prompt Treatment with Epinephrine is Critical

Patient Experiences Symptoms → **Disease Progression**

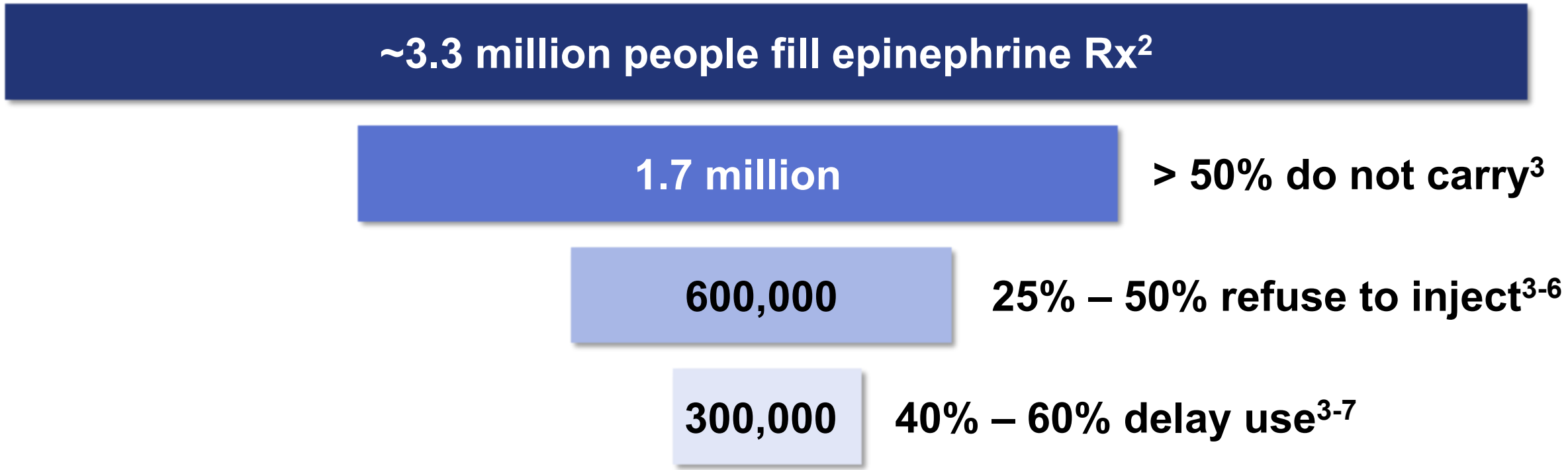
Patients / Caregivers wait up to ~ 18 minutes to dose epinephrine

Consequence of Delayed Treatment	Risk Factor
Abnormal vitals (HR, SBP, Respiration)[1]	p<0.001
Repeat Epinephrine Doses[2]	OR = 5.0
Hospitalization (500,000 ER visits / yr)[3]	HR = 4.0
Biphasic anaphylaxis[4]	OR = 3.4
Fatality[5]	

1. Andrew 2018, Philips 2011; 2. Hochstadter 2016; 3. Fleming 2014; 4. Liu 2020; 5. Turner 2017

Outcomes Impacted by Willingness to Fill, Carry, and Use Epinephrine Needle Devices

- 43% of patients do not fill epinephrine Rx for their needle devices[1]



1. Cohen 2021; 2. IQVIA Claims Data 2022; 3. Warren 2018; 4. Brooks 2018; 5. Asthma and Allergy Foundation of America 2019; 6. Casale 2022; 7. ARS data presented at AAAAI 2023

Needle-Related Safety Risks and Use Errors

- Needle-related risks defined in labeling for all autoinjectors
  - Lacerations and bone injections
  - IV bolus injection (blood vessel injections) – likely result in most serious AEs
- Accidental self-injection into extremity by patient or caregiver
  - ~ 3,500 events per year reported[1]
  - Requires immediate medical attention (treatment in ER typical)
- Injection site pain, infection and other reactions[2]
- Wet injections (withdraw needle too quickly) and other dosing errors
- User errors and device malfunctions[3,4,5]

1. Anshien 2019; 2. Guerlain 2011; 3. El Turki 2017, 4. Moss 2018; 5. FDA (2015, 2017, 2020, 2022)

Epinephrine Needle-Free Options Can Fill Great Unmet Medical Need for Patients and Caregivers

- Epinephrine well-established efficacy and safety profile
  - Systemically acting drug - route of administration should not impact efficacy
  - Efficacy same across epinephrine injection products despite PK differences
- Immediate administration of epinephrine is critical
- Patients and caregivers reluctant to use or carry current devices
  - Needle-phobia
  - Concerns with safety
  - Cumbersome to carry
- Unmet need for needle-free, easy to use, easy to carry, safe and effective epinephrine option

neffy Development Rationale: PK, PD, and Safety Data

Sarina Tanimoto, MD, PhD

Chief Medical Officer and Co-Founder

ARS Pharmaceuticals

neffy Development Program

neffy Clinical Development Program

Completed > 10 clinical trials (Dosed 0.5 to 4 mg)

- ~ 600 subjects treated
- > 1,120 single & twice-dose (up to 4 mg) dosed in healthy volunteers and Type I allergy patient

neffy 1 mg adult studies (Supportive PK/PD studies: EPI 03, 04, 07, 12)

- Single and twice-dose; self-administration; NAC and pollen induced rhinitis
- 1 mg dose equivalent to 0.3 mg IM in adults; now for pediatric 15 kg to < 30 kg
- FDA agreed to increase dose for ≥ 30 kg: Higher exposure within bracket to ensure efficacy

neffy 2 mg adult studies (Primary PK/PD studies: EPI 15, 16, 17)

- Single and twice-dose; self-administration
- Supportive studies in NAC induced rhinitis, infectious rhinitis, dog anaphylaxis model

neffy *1 mg and* 2 mg pediatric PK/PD (EPI 10)

- > 80 patients treated (aged 4 – 17 years)
- Single dose 2 mg in pediatric Type I allergy patients (≥ 30 kg)
- Ongoing single dose 1 mg in pediatrics (15 kg to < 30 kg)

Other Completed or Ongoing Clinical Trials

- EPI 14 (completed): ***neffy*** 2 mg in Upper Respiratory Tract Infection
  - N = 21 subjects with flu, cold, sinus infection or other URTIs
  - Demonstrates no meaningful impact on absorption from congestion and rhinorrhea associated with URTI
- EPI U01 (ongoing): ***neffy*** 1 mg and 2 mg vs placebo in urticaria
  - N = 32 (10 enrolled) refractory urticaria patients
  - Phase 2b efficacy study
- EPI A01 (ongoing): ***neffy*** 1 mg and 2 mg vs albuterol and placebo
  - N = 30 subjects with persistent asthma
  - Phase 2 exploratory

Rationale for Bracketing Approach

Objective: to demonstrate PK comparability across prespecified parameters C_{max}, T_{max}, early partial AUCs (0–20 and 0–45 minutes)

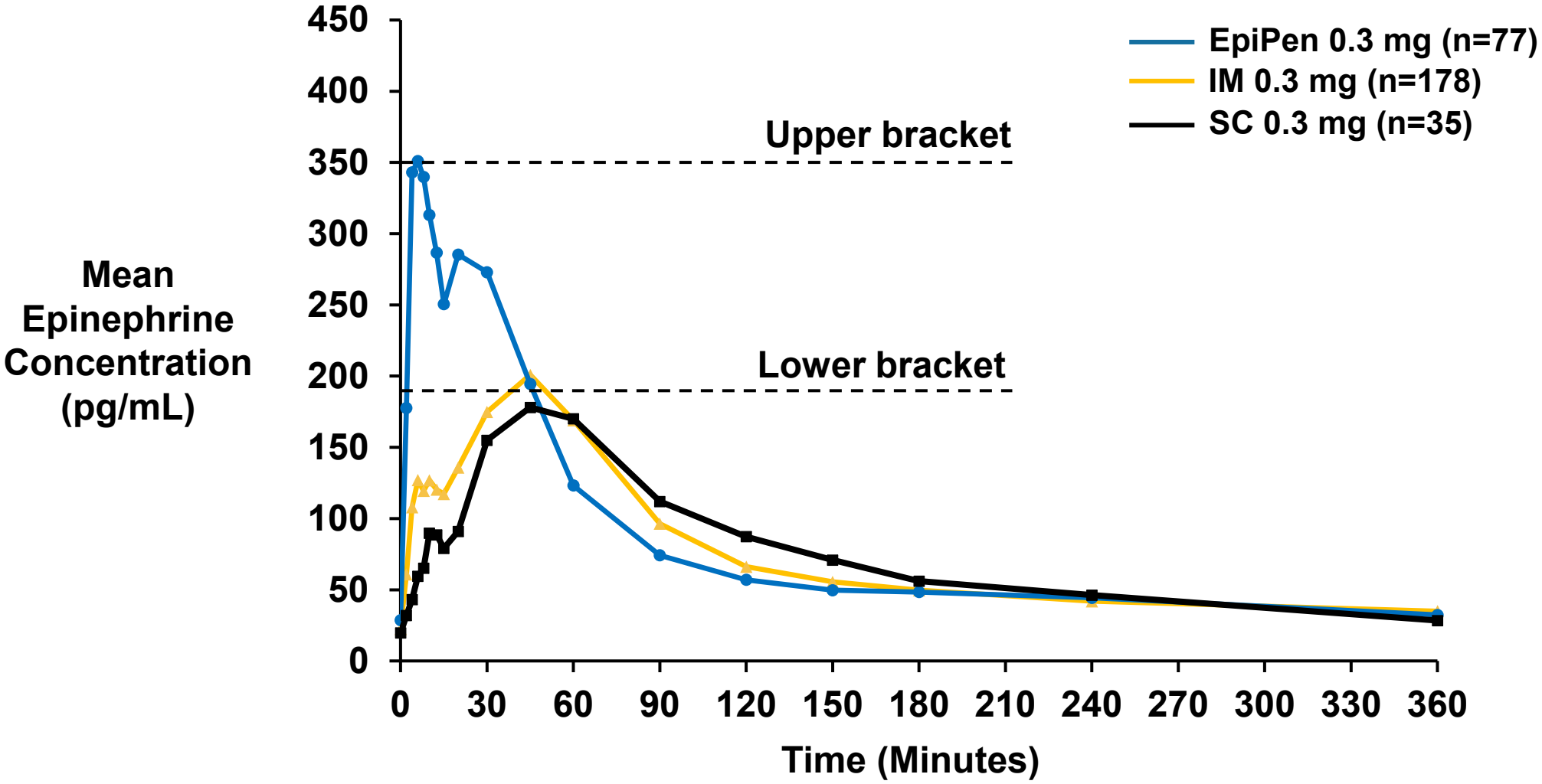
All Products Demonstrate Efficacy Despite Different PK

Treatment[1]	Source	N	Mean Study C_{max} (pg/mL)	Median or Mean Study T_{max} (min)	Study T_{max} Range (min)
EpiPen 0.3 mg	Literature and ARS	507	288 – 869	5 – 40	1 – 240
IM 0.3 mg	Literature and ARS	381	209 – 489	30 to 60	3 – 360
Auvi-Q 0.3 mg	Literature	67	486	20	5 – 60
Symjepi 0.3 mg	ARS data	88	337 – 438	30	4 – 240
SC 0.3 mg	ARS	36	246	45	4 – 180
Total Range			**209 to 869**	**5 to 60**	**1 to 360**

- **Despite PK differences no known difference in efficacy**
- **All products 90% effective on single dose**

1. Srisawat 2022; Aquestive 2022; Edwards 2013; Dworaczyk 2021

ARS Integrated Analysis Confirms PK Profile of IM, SC, and EpiPen

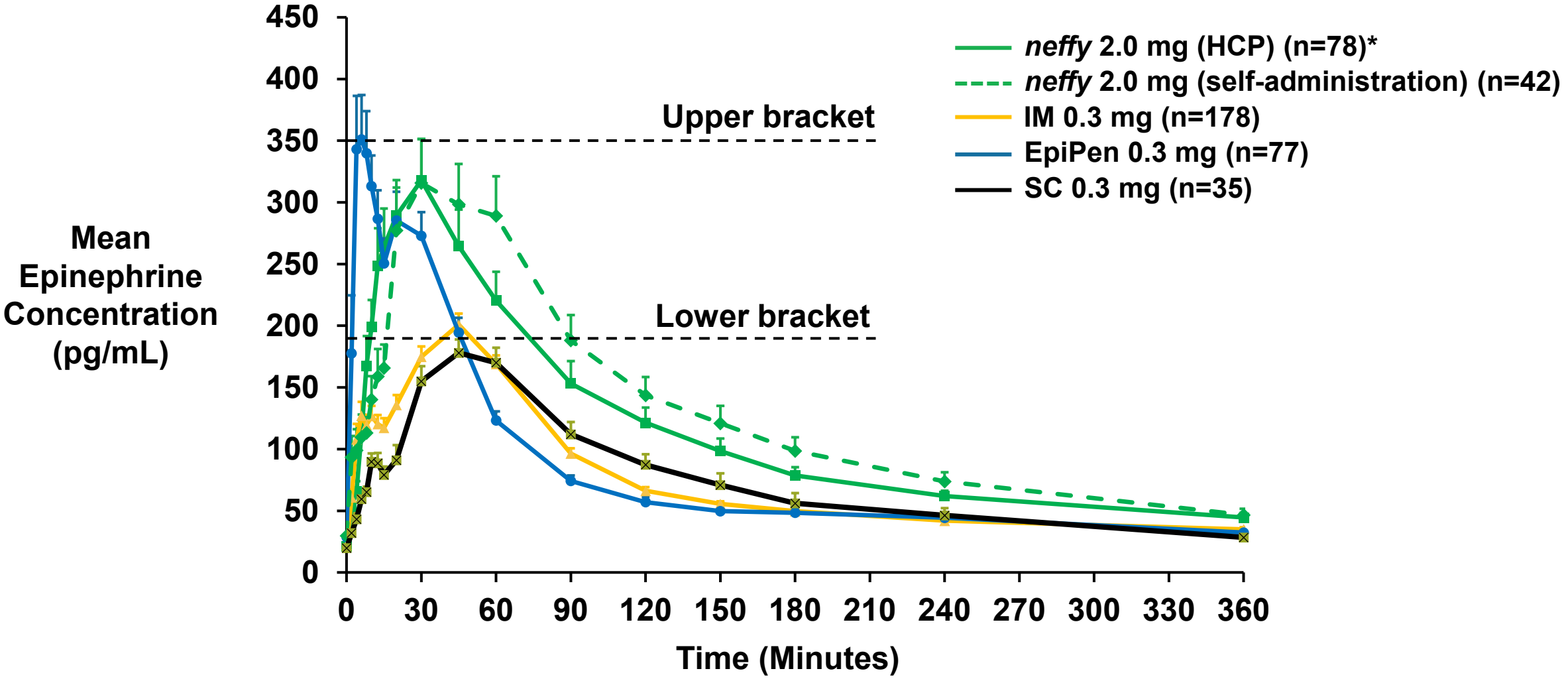


Development Program Focused on Comparison to PK / PD Profile of Approved Epinephrine Products

- PK to ensure efficacious and safe exposures within range of approved products - Bracketing Approach
  - Minimum exposure $\geq$ IM/SC (efficacy)
  - Maximum exposures < EpiPen (safety)
- PD response to support effect at achieving receptor response
  - Blood pressure (BP): α_1 & β_1 (β_2) receptors
  - Heart rate (HR): β_1 receptors

neffy PK Single Administration

Pharmacokinetic Results from *neffy* 2 mg Studies



*Includes Studies EPI-15 and EPI-16

neffy 2 mg Single Dose Bracketed by Injection Across PK Parameters

Product	N	GeoMean C_{max} (pg/mL) (CV%)	Median T_{max} (minutes) (range)	GeoMean $pAUC_{0-20}$ (min*pg/mL) (CV%)	GeoMean $pAUC_{0-45}$ (min*pg/mL) (CV%)	GeoMean AUC_{0-t} (min*pg/mL) (CV%)
SC 0.3 mg	**35**	**214** (55%)	**45** (4–180)	**1,020** (93%)	**4,180** (66%)	**28,400** (37%)
IM 0.3 mg	**178**	**234** (63%)	**45** (4–360)	**1,520** (97%)	**5,260** (68%)	**26,100** (37%)
***neffy* 2 mg – EPI 17** (self-administration)	**42**	**332** (66%)	**30** (6–240)	**2,314** (71%)	**8,491** (63%)	**38,884** (56%)
neffy* 2 mg (HCP)	**78**	**361** (102%)	**20.5** (2–150)	**2,640** (100%)	**8,140** (101%)	**32,600** (81%)
EpiPen 0.3 mg	**77**	**447** (85%)	**10** (2–45)	**4,240** (95%)	**10,200** (64%)	**29,200** (43%)

***Includes Studies EPI-15 and EPI-16; CV = coefficient of variation**

Pediatric Pharmacokinetics (EPI-10 Interim Analysis)

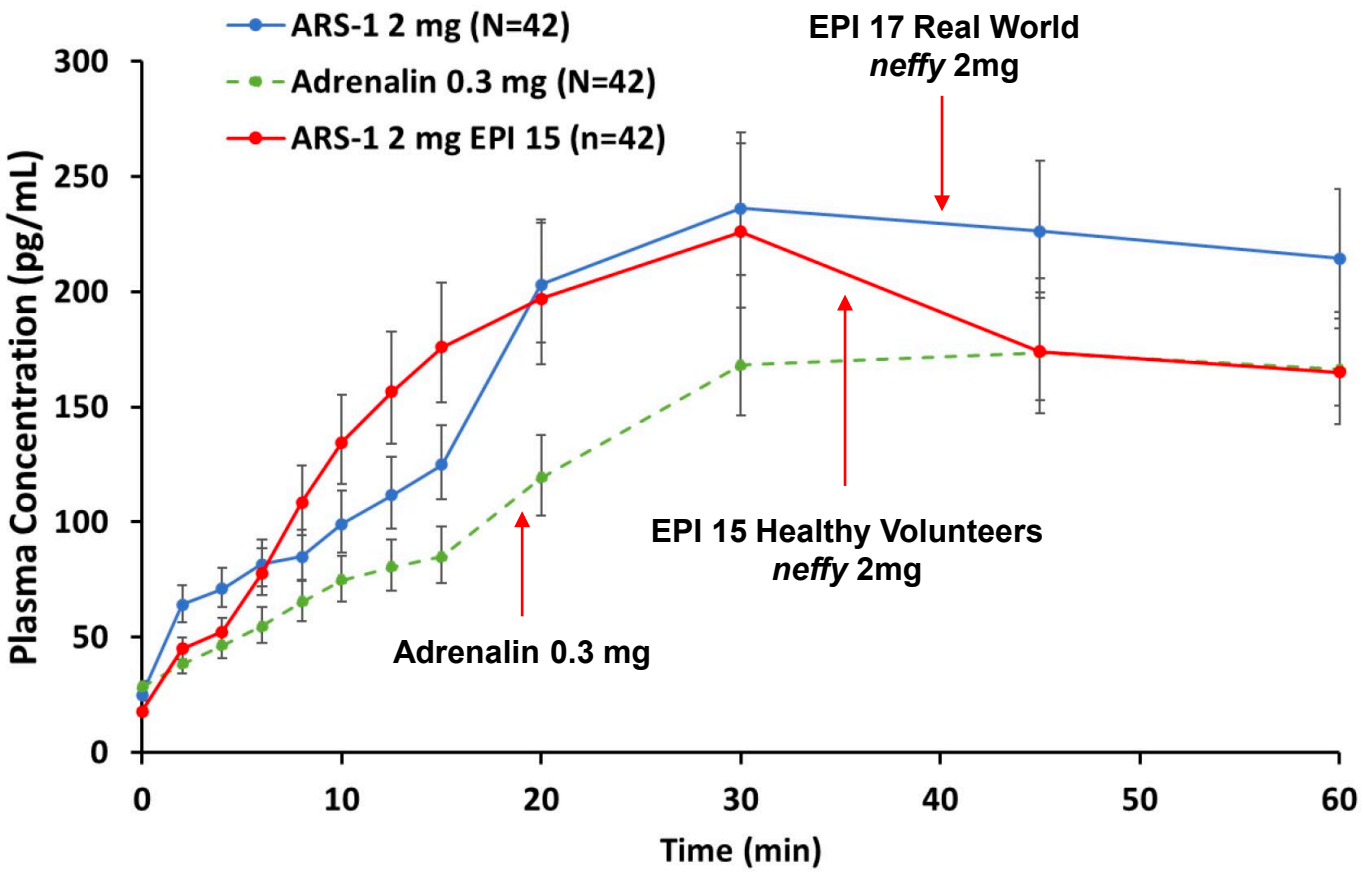
Product	N	GeoMean C_{max} (pg/mL) (CV%)	Median T_{max} (minutes) (range)	GeoMean $pAUC_{0-20}$ (min*pg/mL) (CV%)	GeoMean $pAUC_{0-45}$ (min*pg/mL) (CV%)	GeoMean AUC_{0-t} (min*pg/mL) (CV%)
***neffy* 1.0 mg Children ≥ 30 kg**	**25**	**203** (78%)	**20** (7.5–120)	**2,000** (81%)	**5,100** (67%)	**12,000** (65%)
***neffy* 2.0 mg Children ≥ 30 kg**	**16**	**433** (80%)	**25** (2.5–120)	**3,150** (90%)	**10,900** (73%)	**27,800** (82%)
***neffy* 2.0 mg Adults (EPI 17)**	**42**	**332** (66%)	**30** (6–240)	**2,314** (71%)	**8,491** (63%)	**38,884** (56%)
***neffy* 2.0 mg Adults (EPI 15/16)**	**78**	**361** (102%)	**20.5** (2–150)	**2,640** (100%)	**8,140** (101%)	**32,600** (81%)

- Data supported by Pharmacologically Base Absorption (PBAM) and POP PK Models

neffy PK is Bracketed by EpiPen Studies

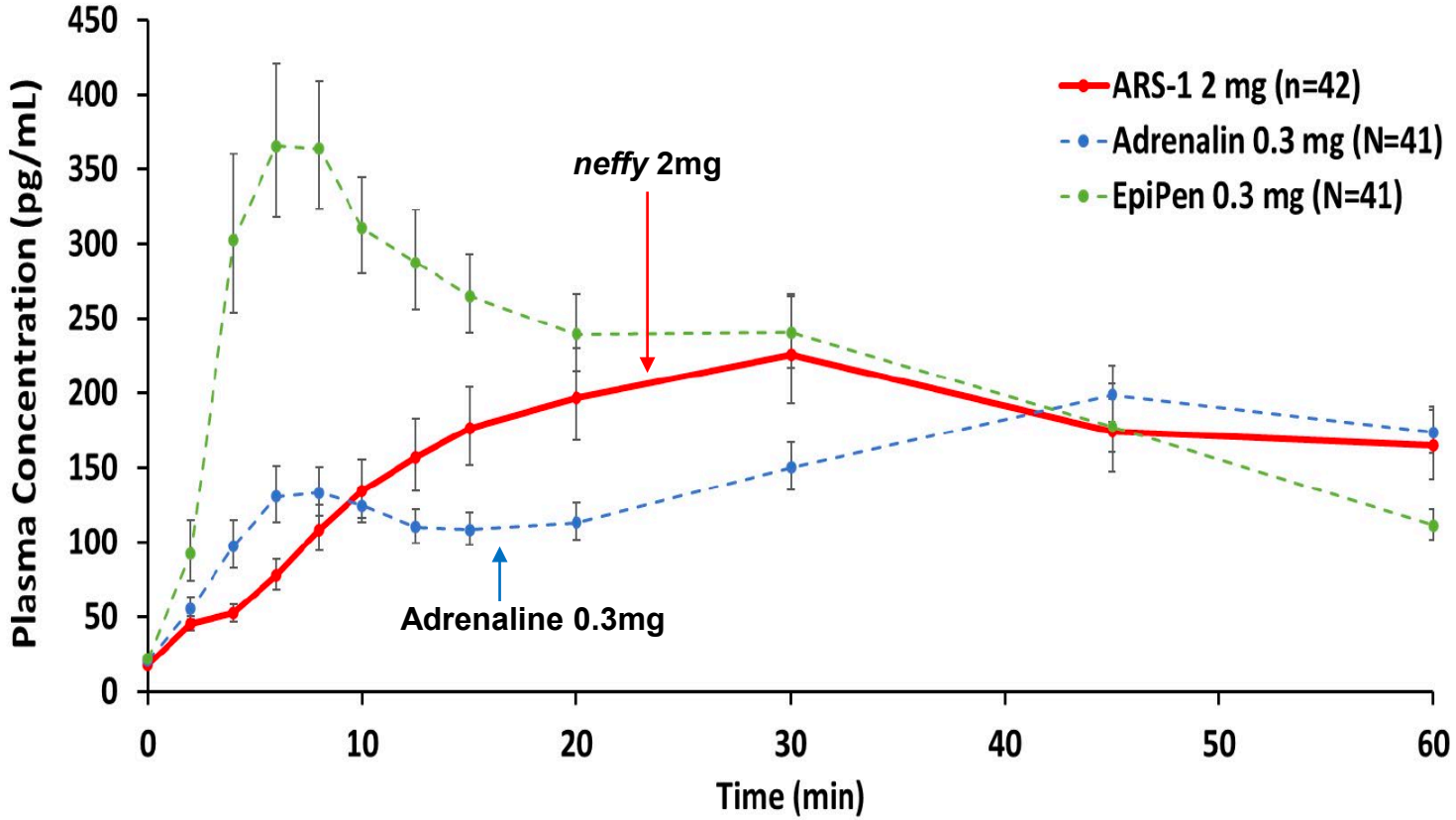
Treatment	Study Reference	N	Mean Study C_{max} (pg/mL)	Median Study T_{max} (min)
EpiPen (0.3 mg)	AQST-109 EPIPHAST II Results (2022)	22	869	22
	ARS EPI-JP01 Data (2020)	30	676	10
	ARS EPI-15 (2022)	35	612	8
	Tal et al. EAACI (2022)	12	550	9
	ARS EPI-11b Data (2021)	9	537	6
	Edwards et al. NDA #201739 (2012)	67	520	10.2
	Chen et al. AAAAI (2019)	11	511	5
	ARS EPI-12 Data (2021)	36	493	8
	ARS EPI-13 Data (2022)	39	490	6
***neffy* (2.0 mg)**	ARS EPI-16 data (2022)	36	491	20
	ARS integrated analysis (2022) – EPI-15/16	**78**	**485**	**20.5**
	ARS EPI-15 data (2022)	42	481	30
	ARS EPI-17 data (2022)	42	421	30
EpiPen (0.3 mg)	Worm et al. Clin Transl Allergy (2020)	12	390 to 530	9 to 30
	Turner et al. Clin Exp Allergy (2021)	37	386	40
	Amphastar US2021/030502 (2021)	56	364 - 458	7-15
	ARS EPI-07 Data (2019)	35	375	24
	Dworaczyk et al. AAAAI (2020)	55	308 to 440	10-16
	Oppenheimer et al. AAAAI (2022)	10	341	22
	ARS EPI-01 Data (2018)	12	333	20
	Aquestive R&D Day (2021)	9	300	10^4
	Dworaczyk et al. AAAAI (2021)	25	288	10

FDA BD Figure 15: Allergy Patients – EPI 17 Self-Administration "Real-World Study" with *neffy* from EPI 15



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 17 and EPI 15.

FDA BD Figure 1: Study EPI 15 – Healthy Subjects: Site Personnel Administration



Source: Clinical Pharmacology Reviewer. Based on adpc.xpt of Study EPI 15.

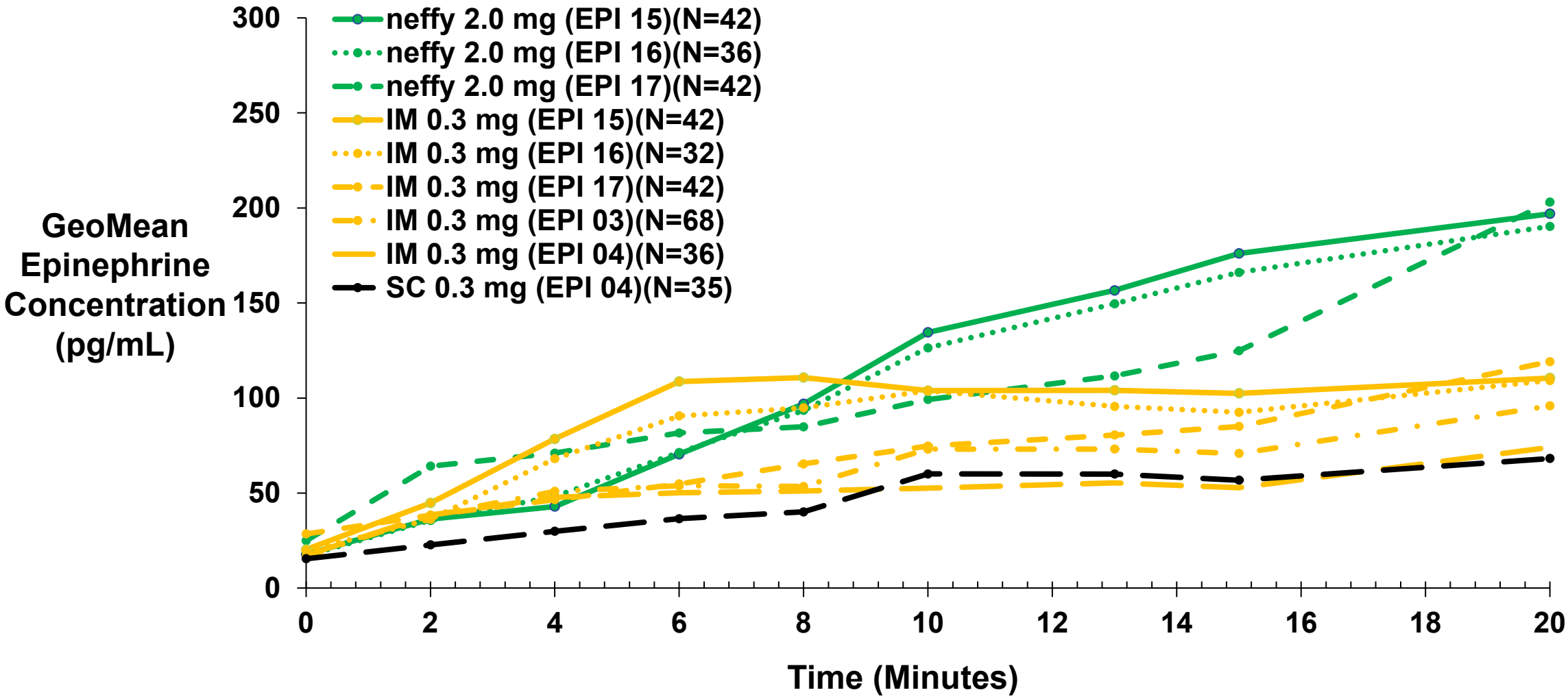
One subject each from the Adrenalin and EpiPen arms was excluded due to an insufficient number of postdose samples (N<3) within 30 mi

neffy Early Exposures Compared to IM 0.3 mg by Geometric Mean

Product	N	GeoMean Total Epinephrine Concentration at Each Time Point (pg/mL) (CV%)							
		2 min	4 min	6 min	8 min	10 min	12.5 min	15 min	20 min
EPI-15: Healthy subjects; HCP administration									
IM 0.3 mg	42	**47** (119)	**79** (175)	**109** (153)	**111** (131)	**104** (106)	**104** (86)	**102** (82)	**111** (80)
***neffy* 2 mg**	42	**36** (94)	**43** (97)	**69** (116)	**97** (131)	**135** (117)	**157** (132)	**176** (121)	**197** (132)
EPI-17: Type I allergy patients; self-administering neffy (real-world study)									
IM 0.3mg	42	**38** (88)	**47** (107)	**55** (112)	**65** (109)	**75** (105)	**81** (107)	**85** (113)	**119** (120)
***neffy* 2 mg self-admin**	42	**64** (95)	**71** (91)	**82** (95)	**85** (97)	**99** (107)	**112** (110)	**125** (98)	**203** (103)
EPI-16: Seasonal allergic rhinitis patients; site personnel administration (nasal allergen challenge)									
IM 0.3 mg	35	**36** (106)	**68** (143)	**84** (176)	**95** (136)	**104** (126)	**96** (128)	**93** (137)	**109** (114)
***neffy* 2 mg**	36	**37** (120)	**48** (112)	**71** (155)	**93** (195)	**126** (132)	**150** (150)	**166** (133)	**190** (131)

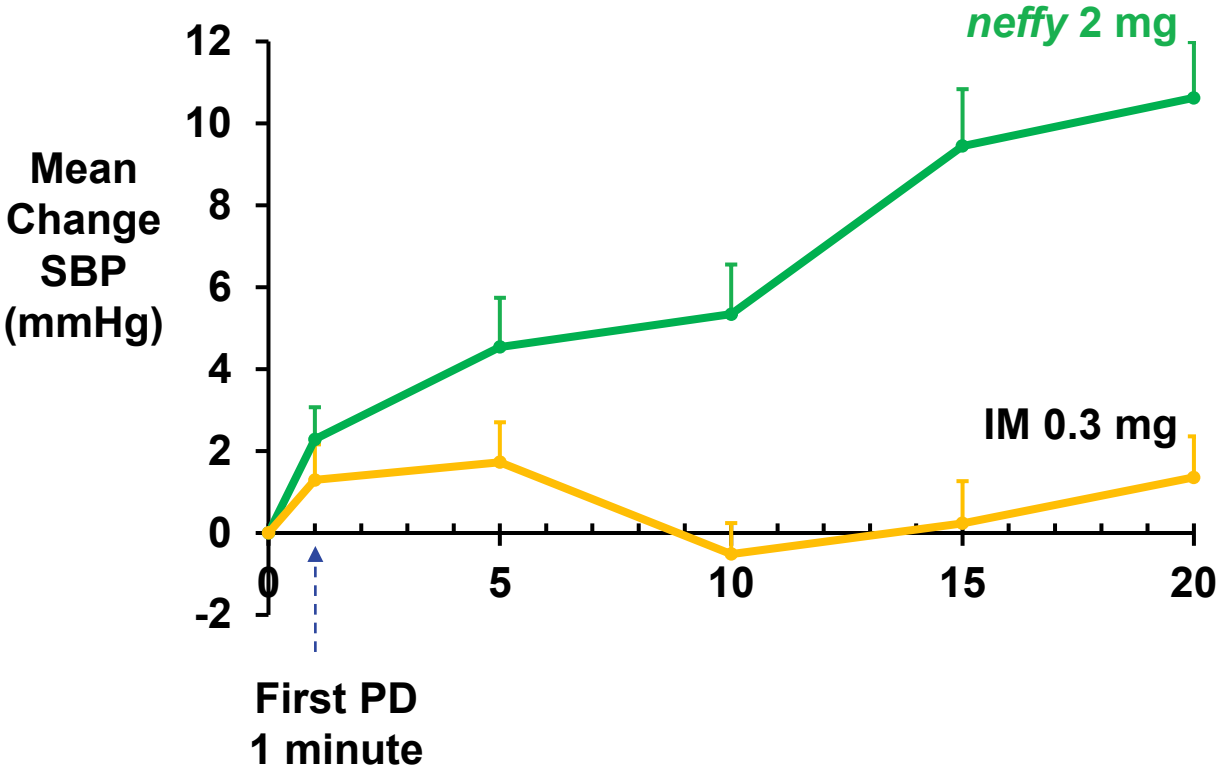
Note: Statistically Different Results Highlighted in Yellow

neffy PK Data Within Bracket of IM and SC Exposures (FDA Approved Dosing)

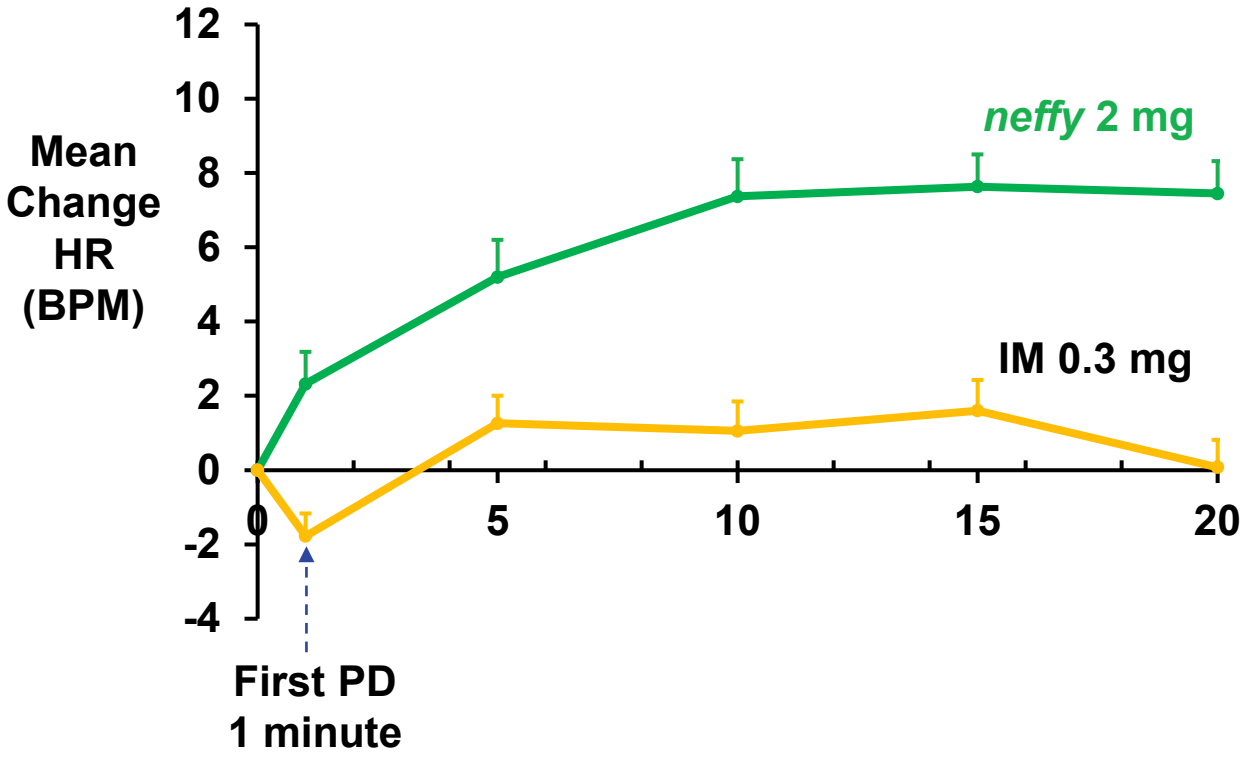


Pharmacodynamic Response Observed (First 20 minutes)

Systolic Blood Pressure Response



Heart Rate Response

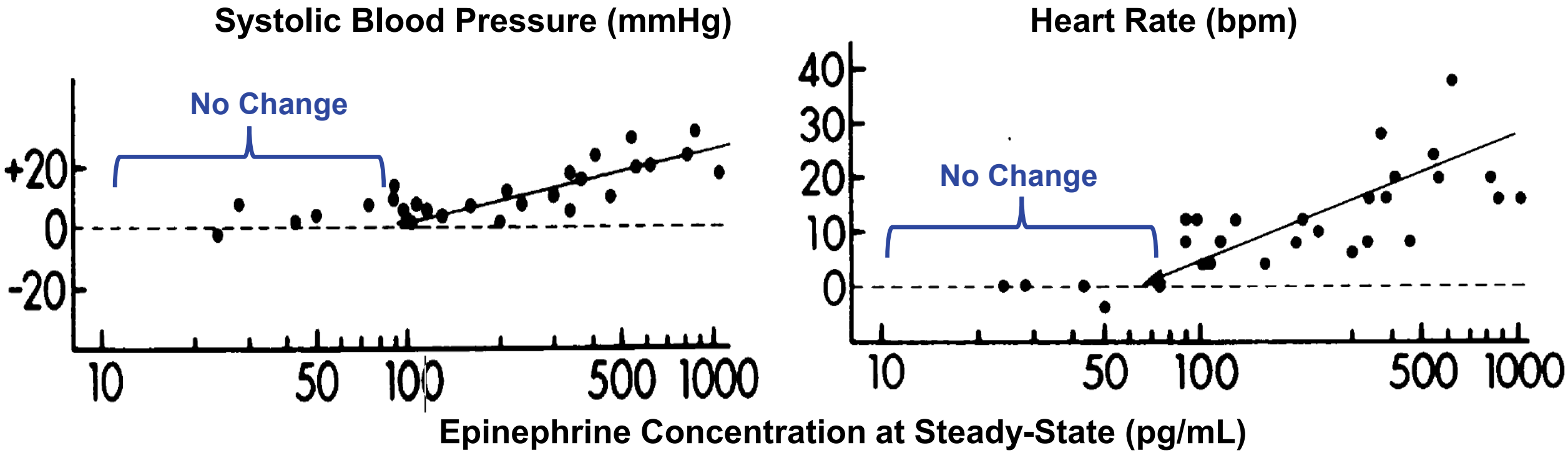


Integrated data Studies EPI 15 and EPI 16

Epinephrine Concentration of 100 pg/mL

Single Source of 100 pg/mL for SBP: Clutter (1980)

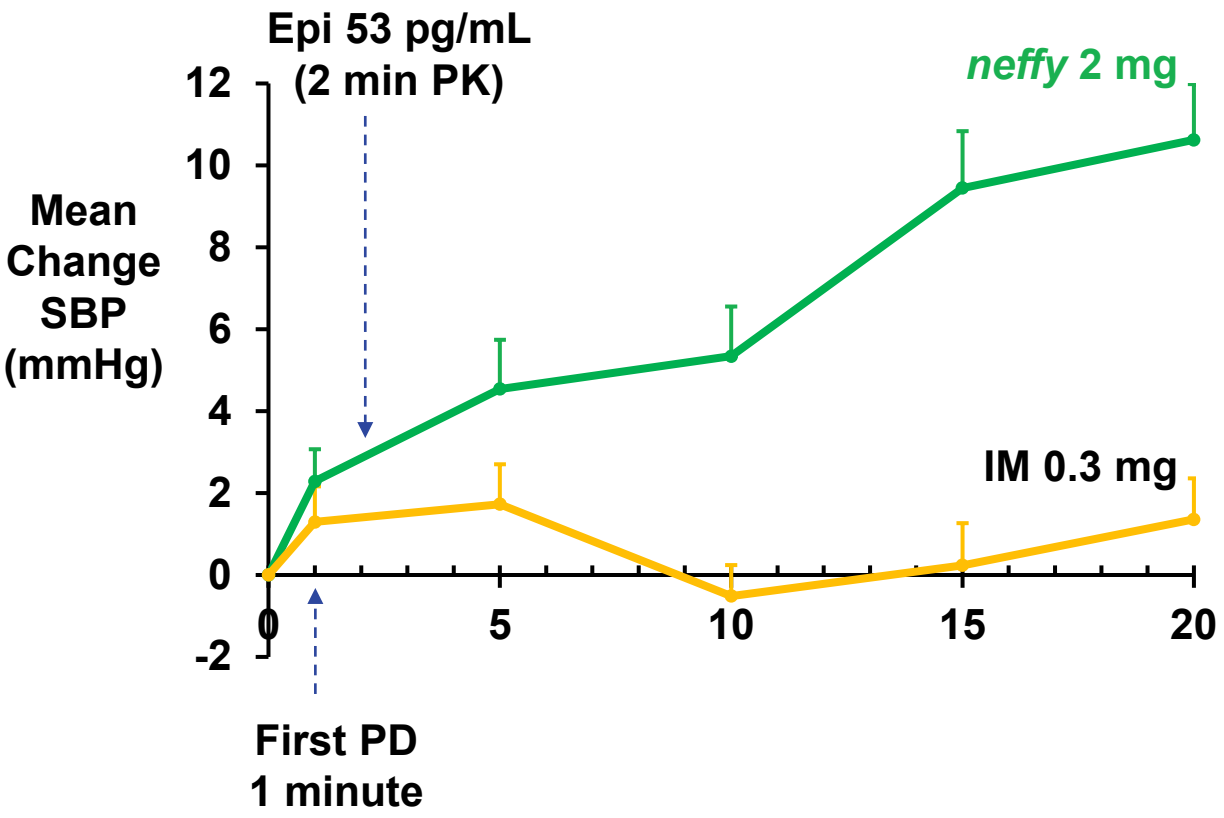
- **6 healthy subjects; continuous IV study** at 60-min 0.1, 0.5, 1.0, 2.5, and 5.0 μg/min
- **5 – 15 min intervals** before and during each infusion
  - Continuous IV allows time for body to adapt to epinephrine and HR/SBP changes



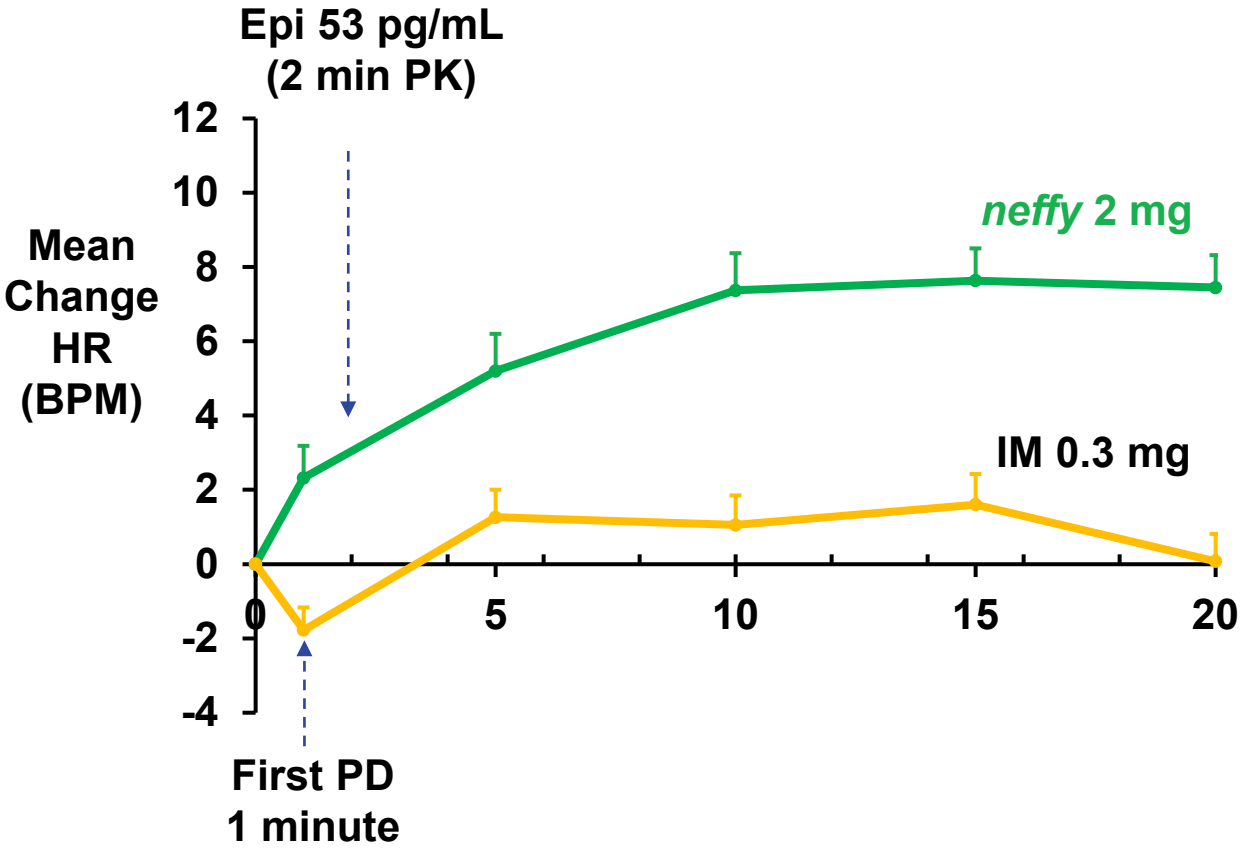
This finding has not been replicated in any other published literature

Pharmacodynamic Response Observed (First 20 minutes)

Systolic Blood Pressure Response



Heart Rate Response



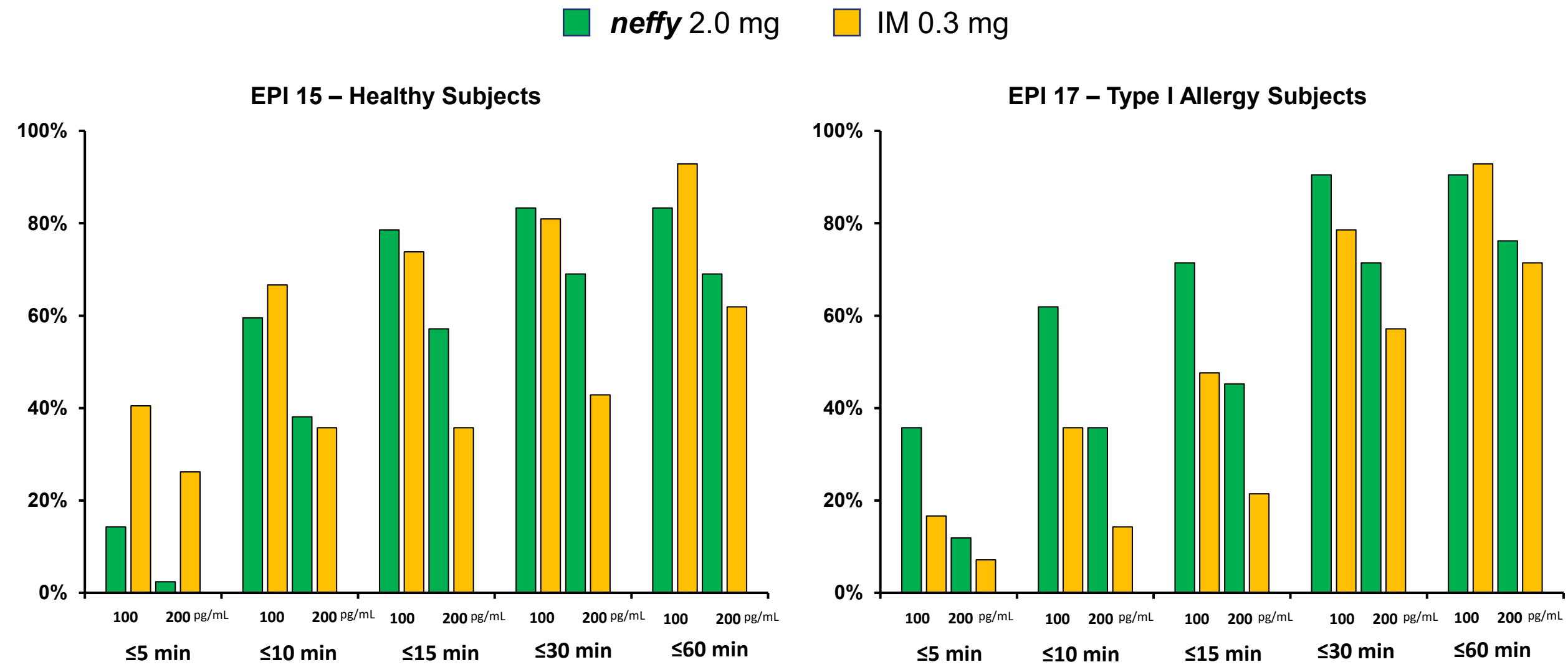
Integrated data Studies EPI 15 and EPI 16

Proportion of Subjects Reaching C_{max} ≥ 100 pg/mL in 60 minutes Comparable Between Injection and *neffy*

Treatment	Study	% Patients ≥ 100 pg/mL (once)
IM 0.3 mg	EPI 03	84%
	EPI 04	97%
	EPI 15	95%
	EPI 16	94%
	EPI 17	90%
	EPI JP 02	92%
SC 0.3 mg	EPI 04	91%
Symjepi 0.3 mg	EPI 12	91%
EpiPen 0.3 mg	EPI 07	97%
	EPI 12	90%
	EPI 15	100%
***neffy* 2 mg (ARS-1)**	EPI 15	83%
	EPI 16 normal	94%
	EPI 16 rhinitis	94%
	EPI 17	90%
	EPI JP 02	100%
	EPI 14 normal	100%
	EPI 14 URTI	100%

- Across studies percent of subjects achieving threshold exposures is similar
  - 100 pg/mL
    - 84% to 100% for injection products
    - 83% to 100% for ***neffy*** 2 mg

Proportion of Subjects Reaching 100/200 pg/mL



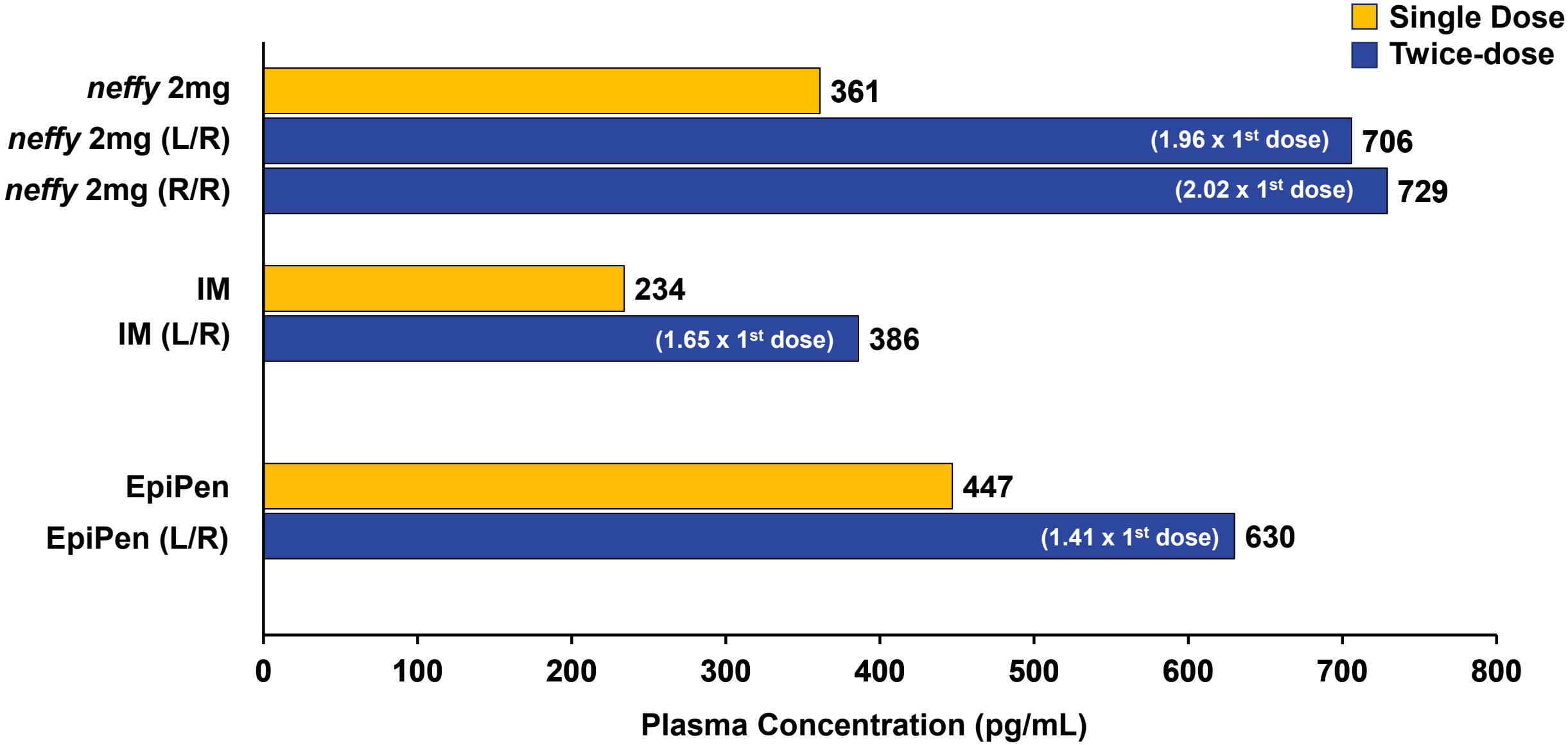
neffy PK for Twice Dosing (4 mg):
Dose Proportional PK

Second Dose May be Required in More Severe Cases

- Second dose of epinephrine required ~10% of time regardless of injection device used[1]
- More severe allergic reactions need higher exposures to ensure efficacy[2]
- Hypotension greater concern in severe cases or when treatment is delayed and disease progression occurs[3,4]
- No bracketing criteria for a second dose

1. Patel 2021; 2. Sicherer 2017; 3. Blazowski 2021; 4. Ko 2016

neffy Dose Proportionality (Geometric Mean C_{max})

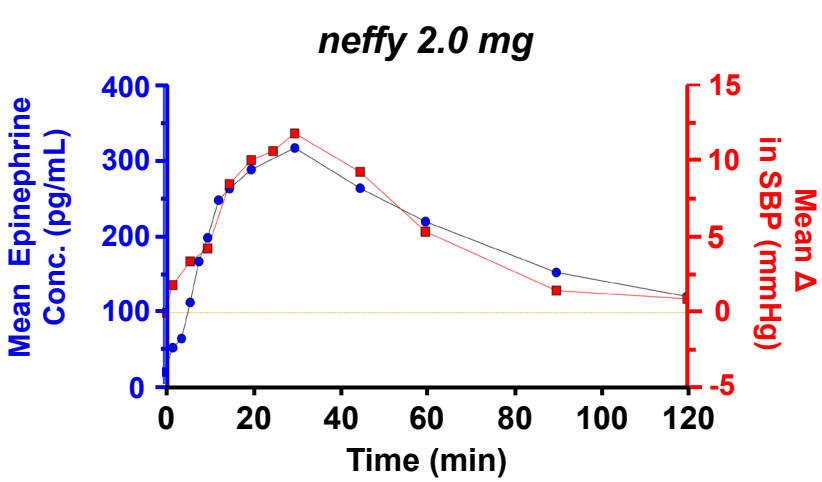


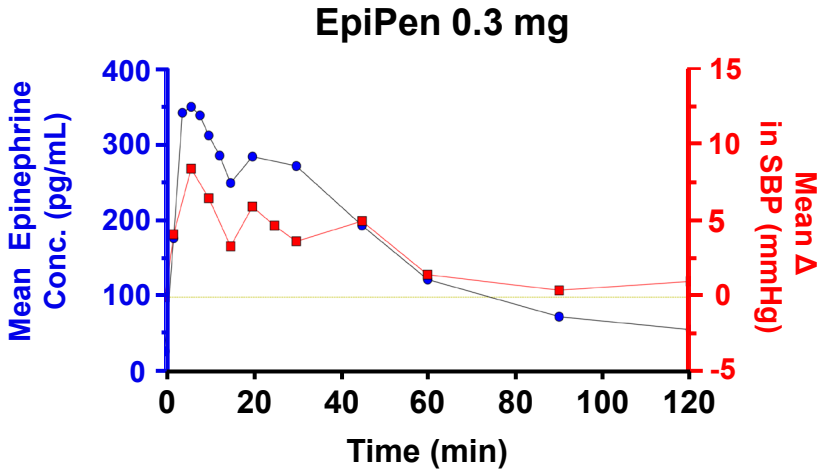
PK Conclusions: *neffy* 2 mg Within Bracket of Approved Injection Products

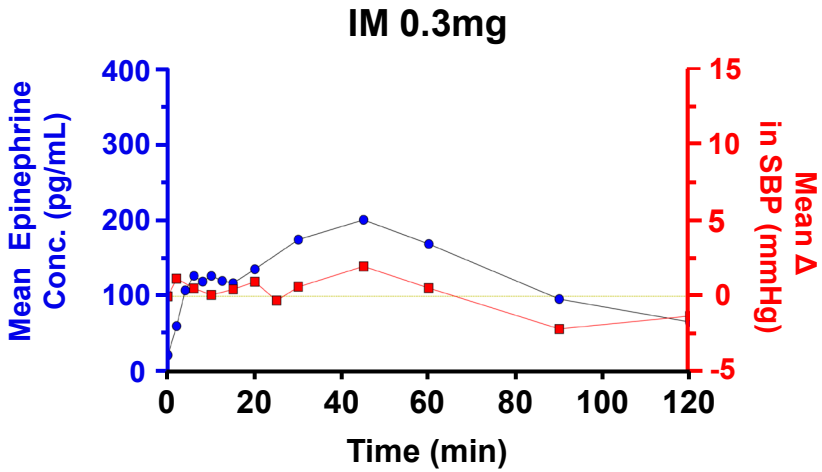
- Basis for efficacy and safety
  - ***neffy*** more rapid and greater exposures vs IM / SC 0.3 mg overall
  - No real difference in first 10 minutes; PD greater for ***neffy***
  - ***neffy*** lower $C_{max,}$ more consistent PK vs EpiPen
- ***neffy*** dosed twice achieves dose proportional increase in exposure for more severe allergic reactions
  - Injections less than dose proportional, lower PK on second dose
- ***neffy*** in pediatric subjects ≥ 30 kg consistent with adults and dose proportional between 1 mg and 2 mg
  - Modeling supports that exposures are bracketed by injection

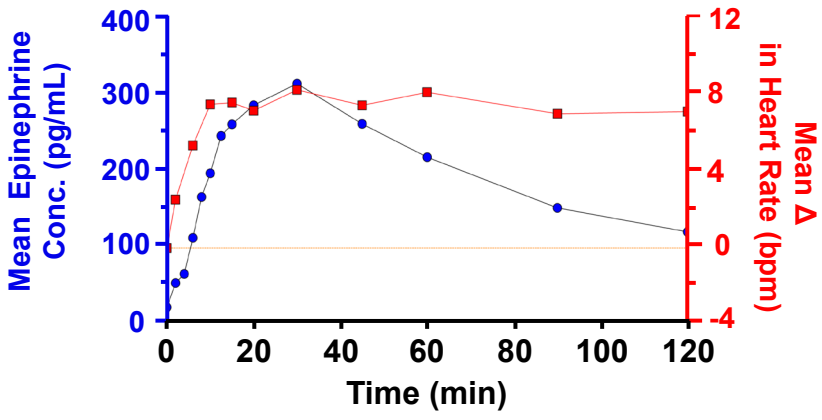
PK / PD Correlation with *neffy*

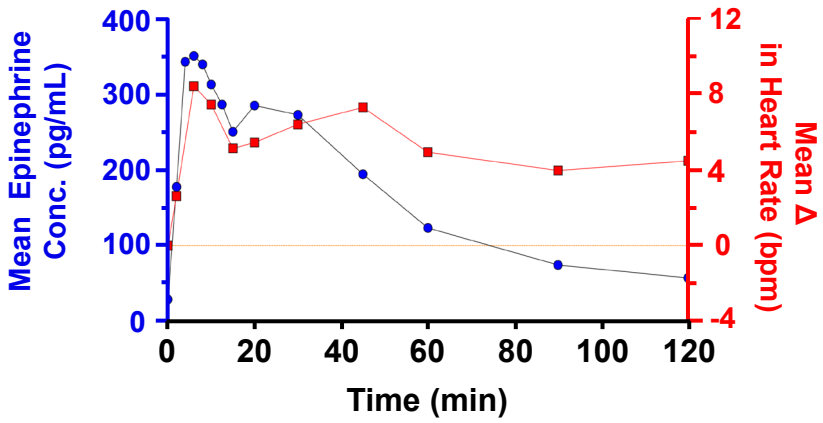
Statistically Significant PK Correlation with SBP and HR ($p < 0.0001$ for All Comparisons)

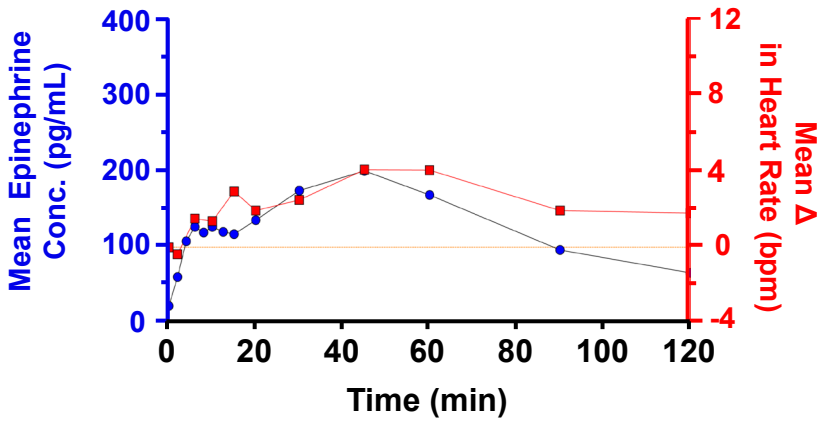












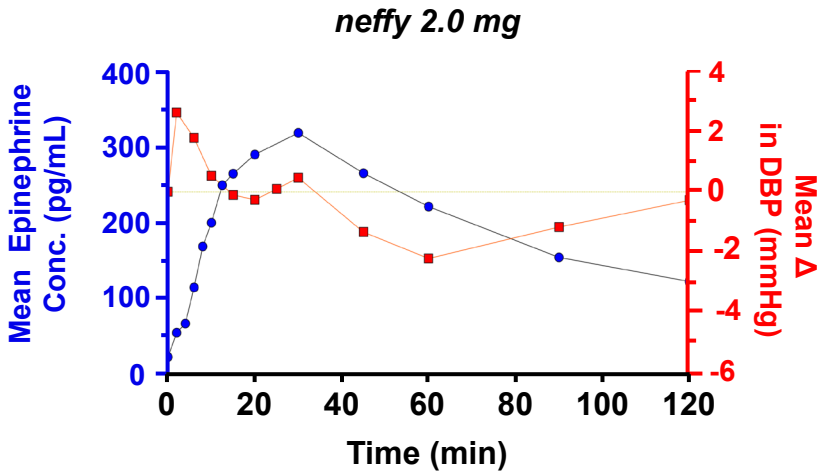
N=78

N=77

N=142

PK / PD Correlation – Inverse or Inconsistent for DBP

- β_2-mediated vasodilation in skeletal muscle causes DBP decrease
- Effect is greater with injection into skeletal muscle vs. other routes of administration (IV / Intranasal)



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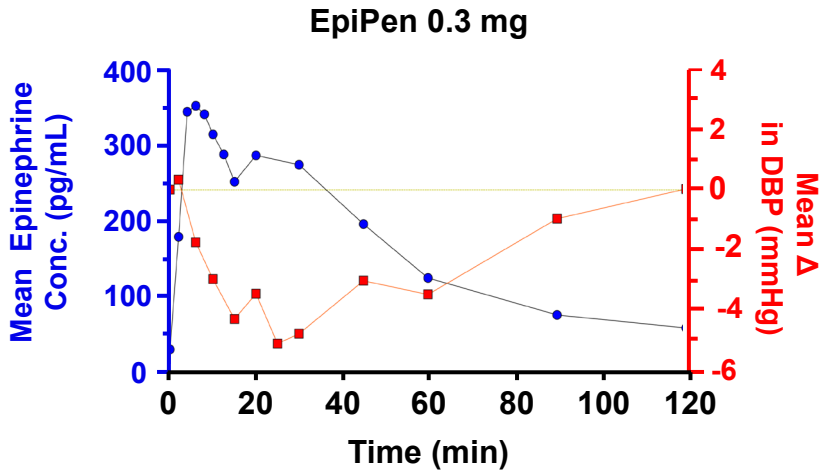
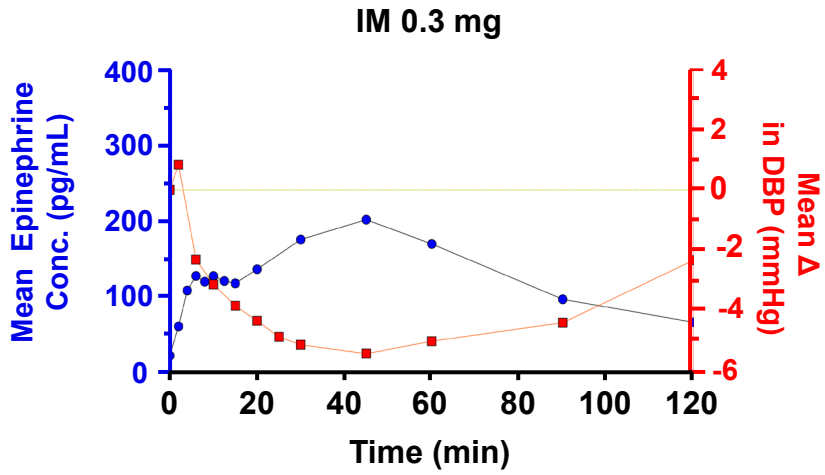


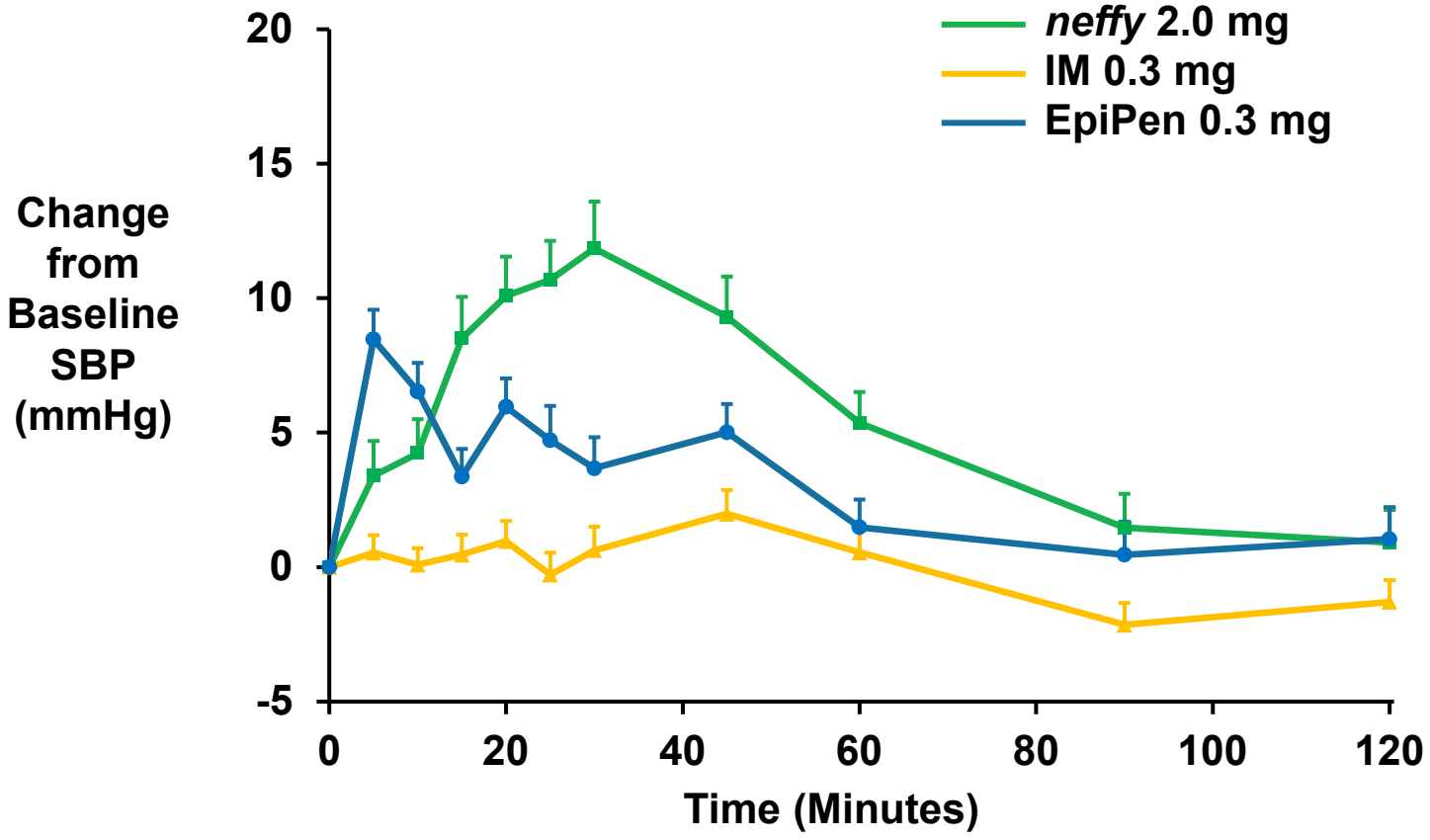
N=77

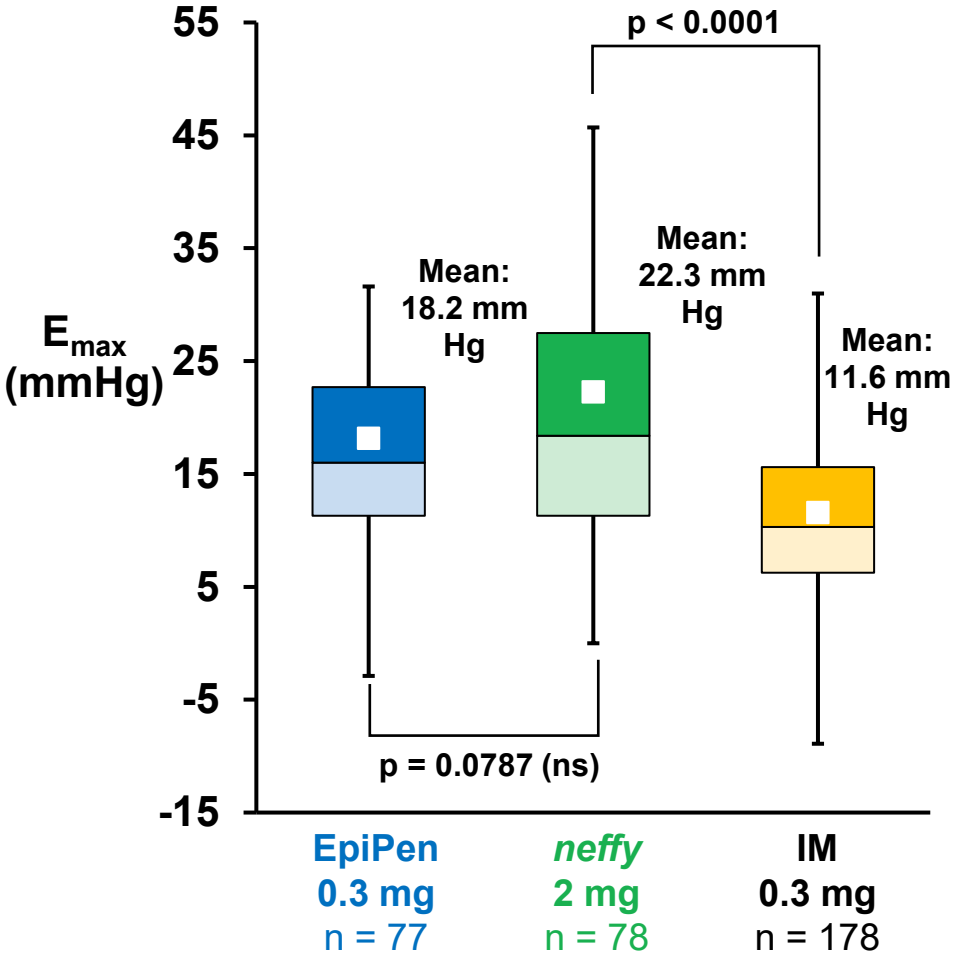


N=142

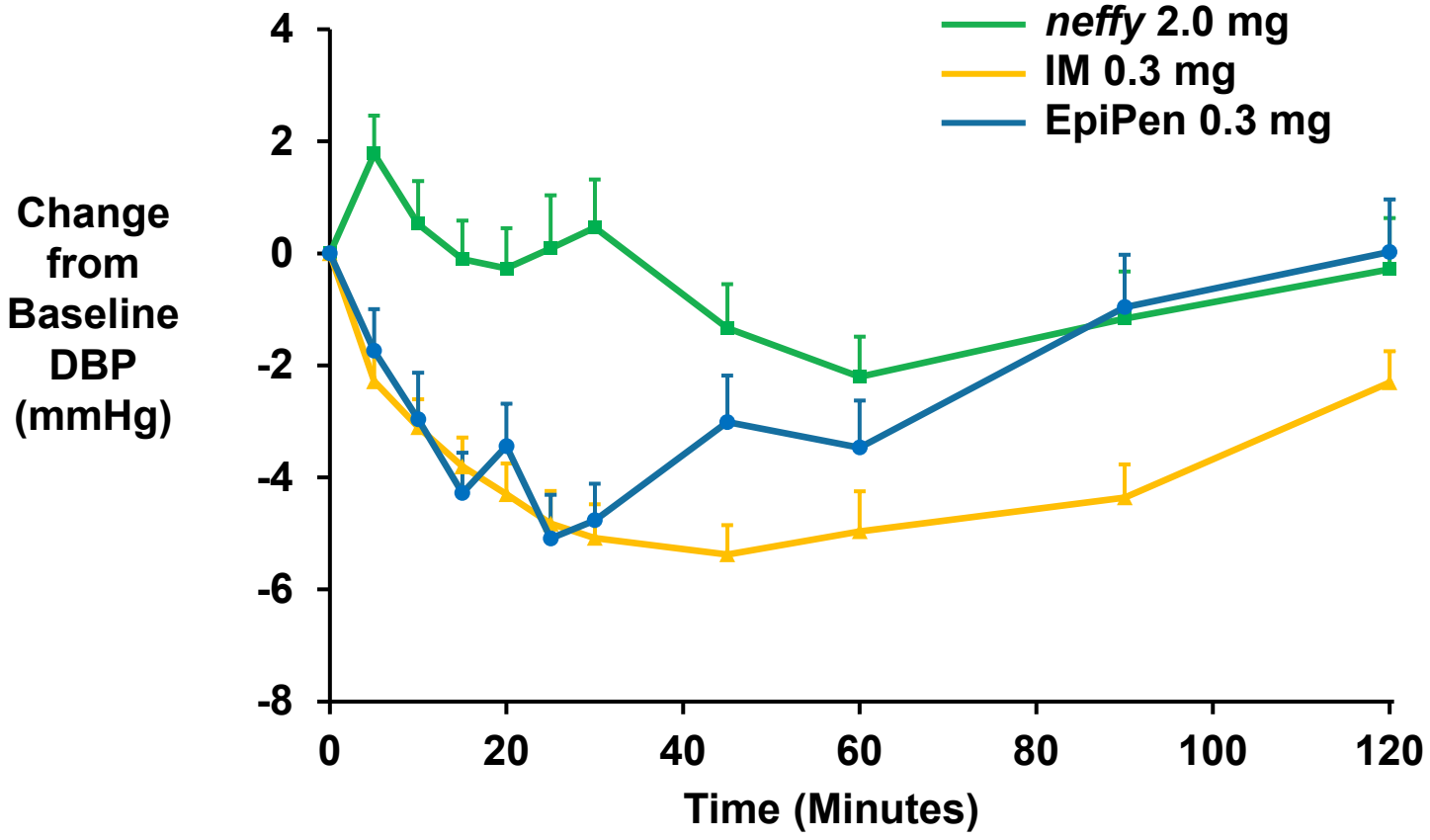
neffy PD Data Comparable or Better than to Injection

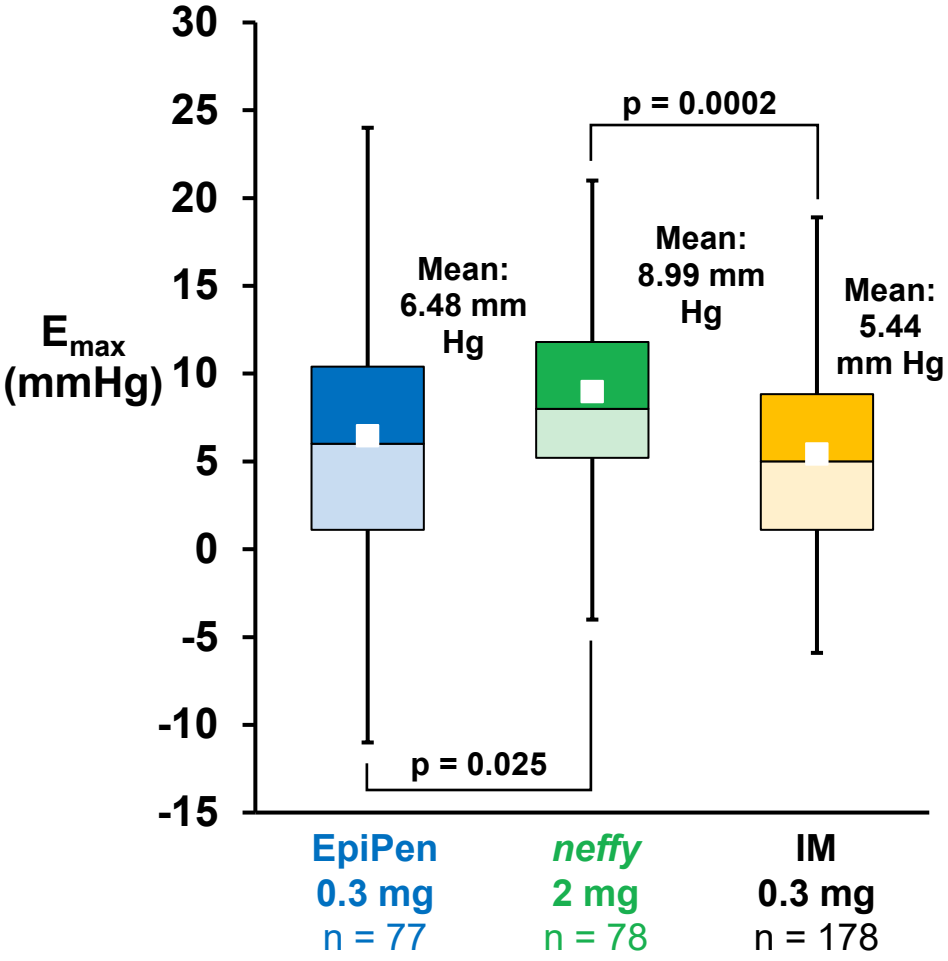
Mean SBP Response from Single *neffy* 2 mg Comparable to or Better than Injection Products



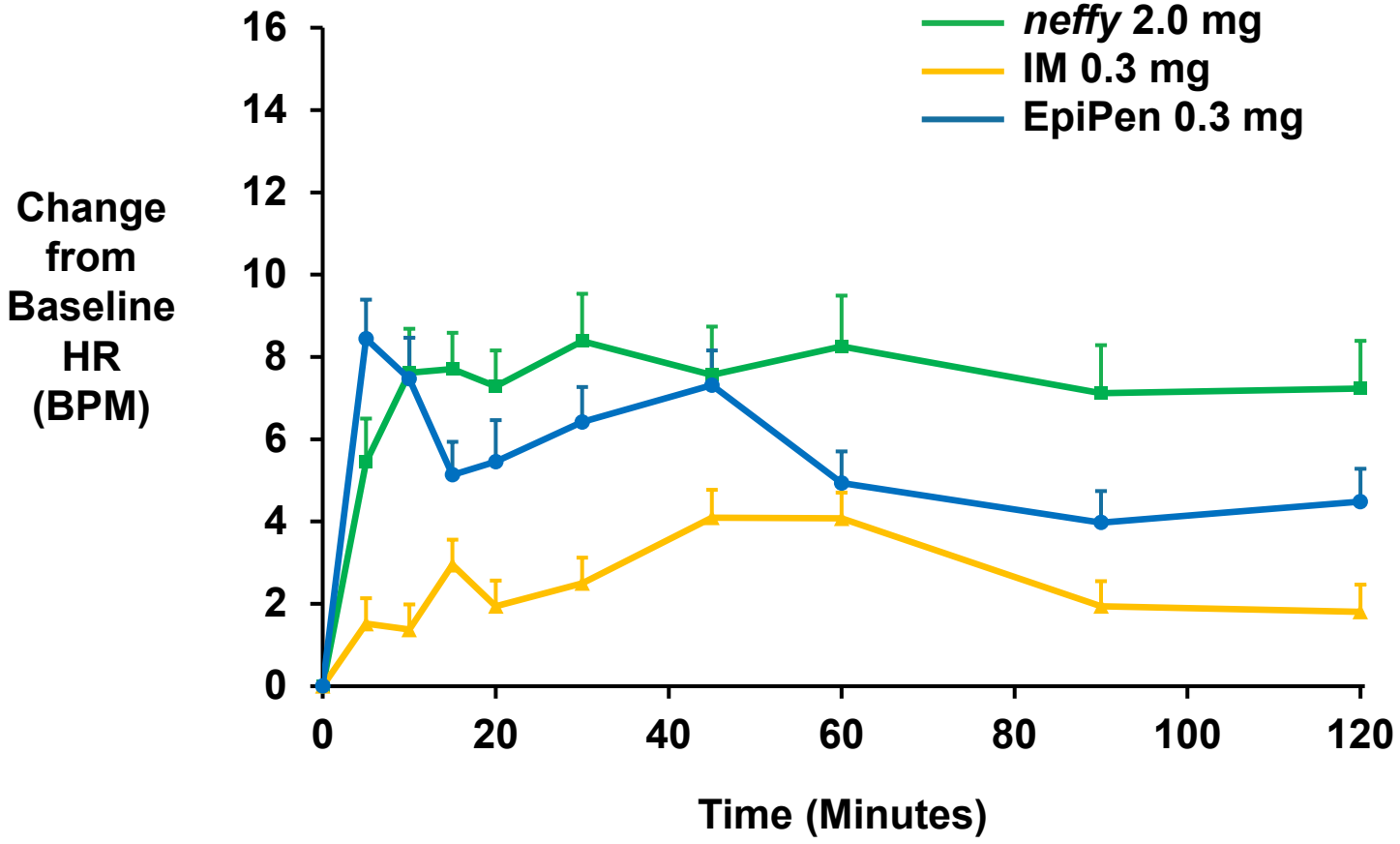


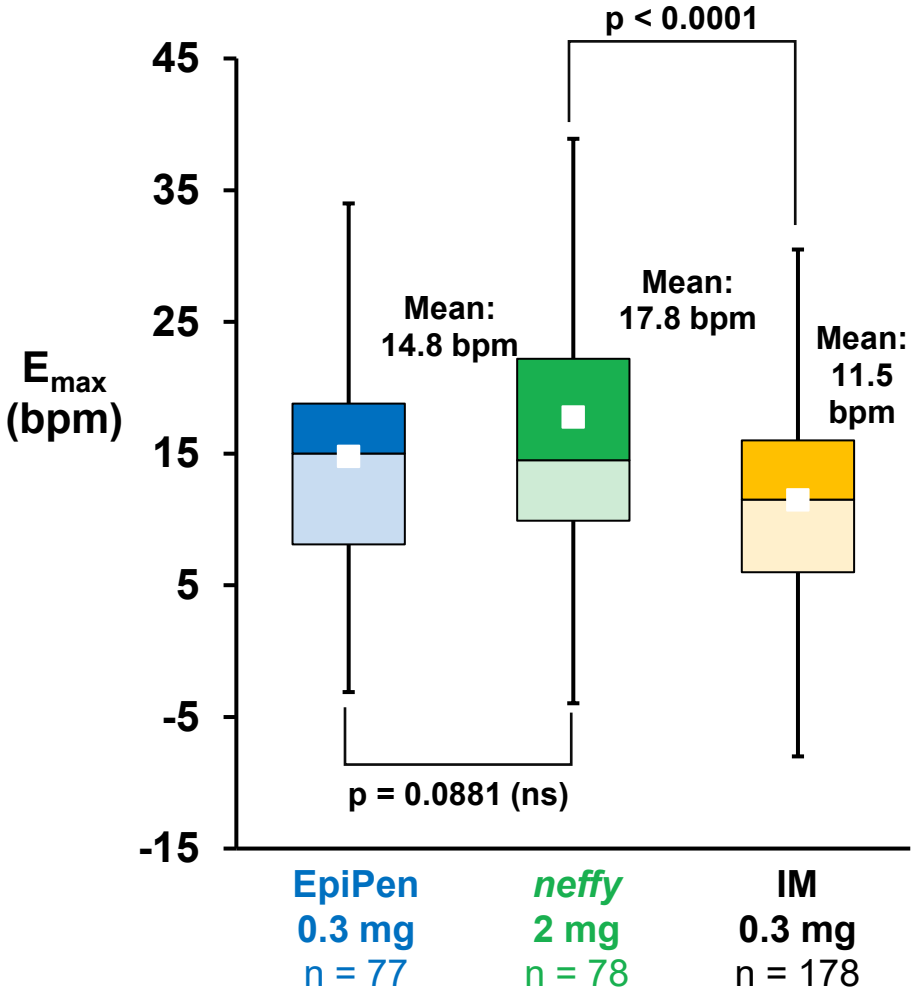
Mean DBP Change for Single 2 mg *neffy* Demonstrates Less Early Decrease than Injection Products



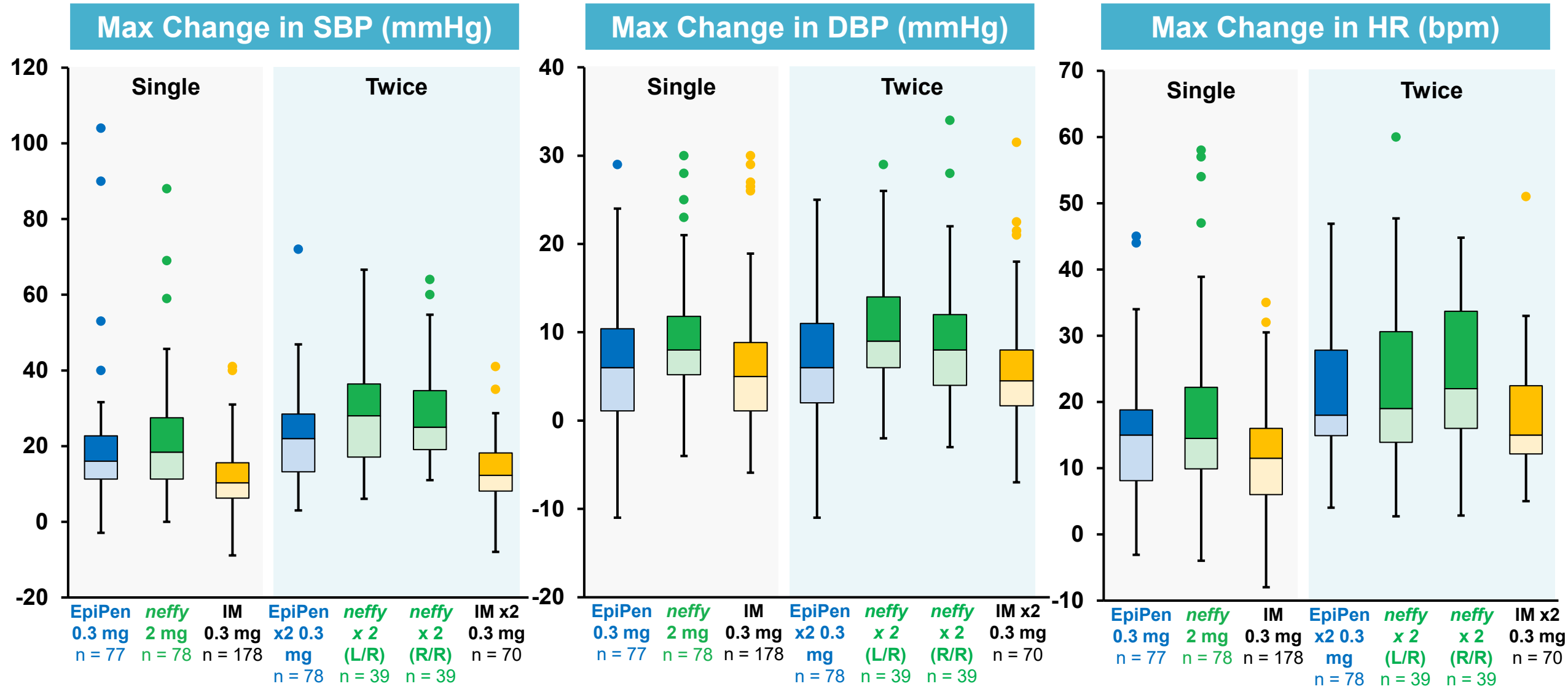


Mean HR Response from a Single 2 mg *neffy* is Comparable to or Better than Injection Products





neffy PD: Comparable Maximum Changes

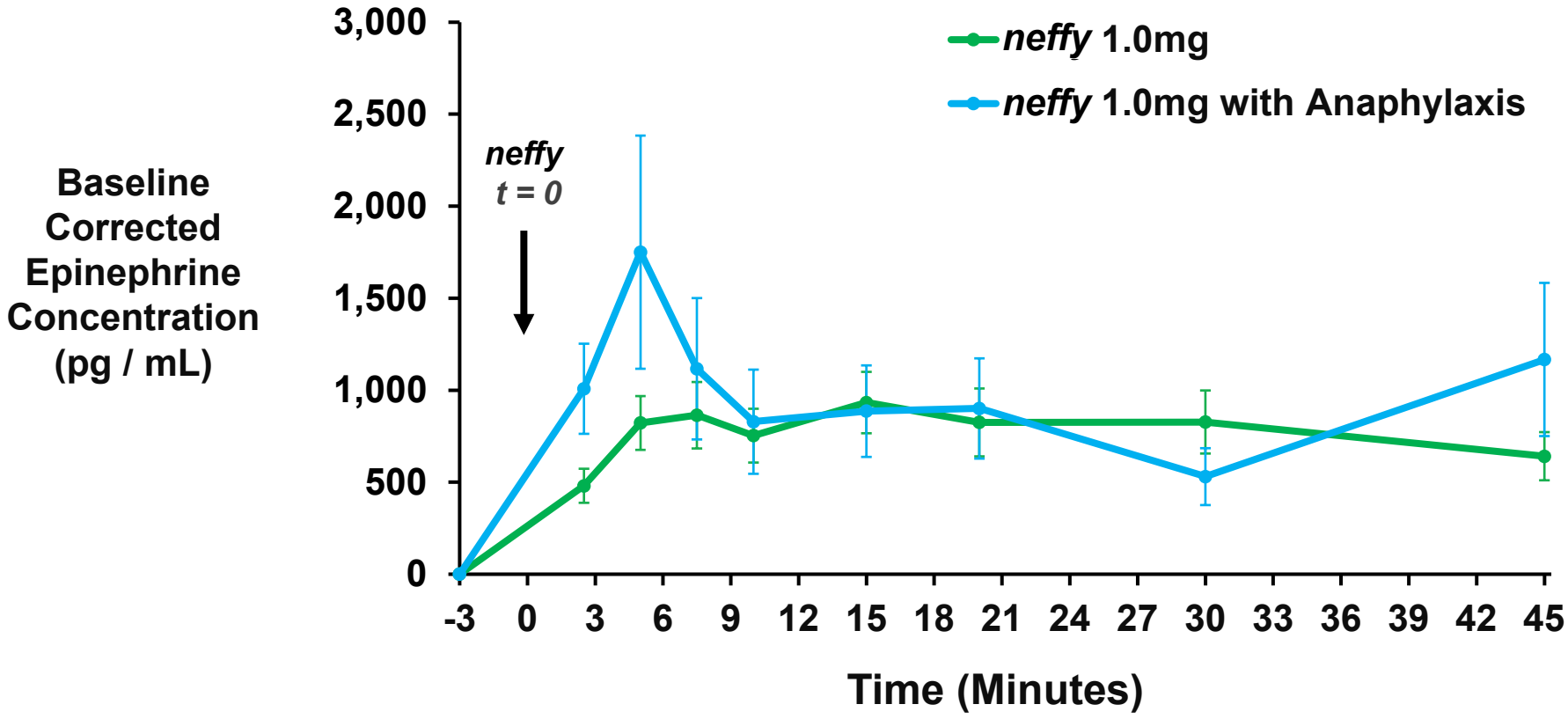


Additional Studies to Support Nasal Administration

Studies to Challenge Nasal Administration

- Dog Anaphylaxis Model
  - Impact of anaphylaxis with severe hypotension and facial edema on nasal absorption
- Nasal Allergen Challenge Study (NAC) (EPI 16)
  - Impact of NAC induced rhinitis on absorption of epinephrine
- Upper Respiratory Tract Infection (URTI) (EPI 14)
  - Impact of URTI on absorption of epinephrine

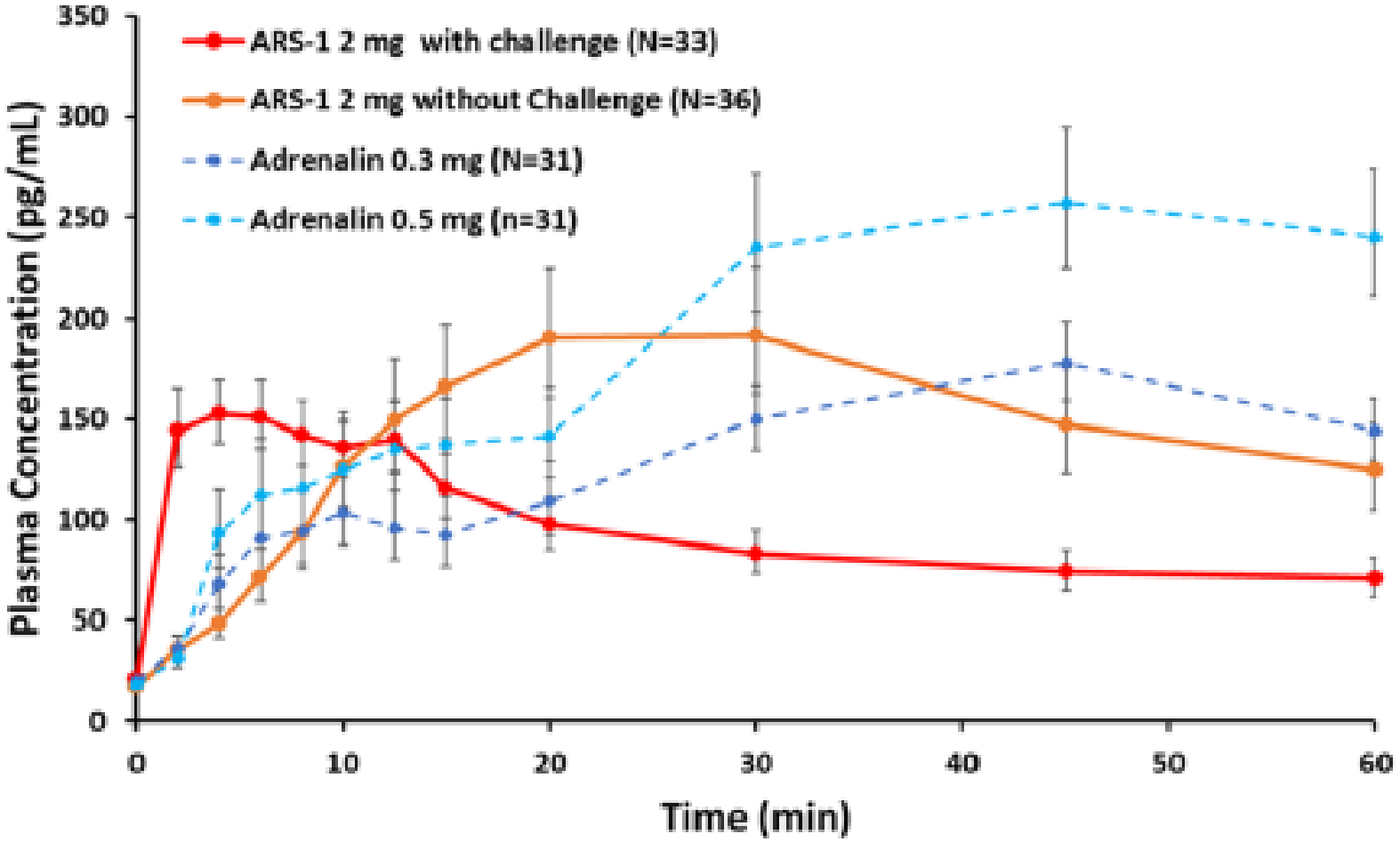
Dog Anaphylaxis Model: Absorption During Hypotension



- N = 14 normal / 12 anaphylaxis
- Absorption during hypotension confirmed (mean animal BP 61±10 / 39±7 mmHg)
- Potentially improved absorption during anaphylaxis increased permeability in allergic reaction

FDA BD Figure 2: EPI 16 - Nasal Allergen Challenge Induced Rhinitis

Figure 2. Epinephrine Geometric Mean (±Standard Error) Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis



Nasal Allergen Challenge PK Results (EPI 16)

Treatment	N	T_{max} (min) **Median** (range)	GeoMean C_{max} (pg/mL) (CV%)	GeoMean AUC_{last} (min*pg / mL) (CV%)
***neffy* 2.0 mg**	**36**	**20** (2 – 120)	**386** (90%)	**29,400** (88%)
***neffy* 2.0 mg rhinitis**	**34**	**7** (2 – 90)	**252** (66%)	**19,600** (63%)
IM 0.3 mg	**35**	**45** (4 – 360)	**213** (77%)	**23,800** (46%)

- Edema (congestion) results in more rapid absorption vs normal nasal conditions
- Rhinorrhea may cause more rapid drainage, drug cleared more quickly (lower C_{max} and AUC vs normal nasal conditions)
- C_{max} greater and T_{max} more rapid than IM 0.3 mg injection

neffy with NAC Induced Rhinitis Gives Higher Exposures Compared to IM Through Relevant Period of Effect (EPI 16)

Product	N	GeoMean $pAUC_{0-10}$ (min*pg/mL) (CV%)	GeoMean $pAUC_{0-15}$ (min*pg/mL) (CV%)	GeoMean $pAUC_{0-20}$ (min*pg/mL) (CV%)	GeoMean $pAUC_{0-30}$ (min*pg/mL) (CV%)	GeoMean $pAUC_{0-45}$ (min*pg/mL) (CV%)
***neffy* 2 mg rhinitis**	**34**	**1,370** (66%)*	**2,110** (63%)*	**2,700** (63%)*	**3,700** (62%)*	**5,030** (60%)
IM 0.3 mg normal	**35**	**646** (135%)	**1,080** (137%)	**1,530** (134%)	**2,710** (116%)	**4,850** (103%)

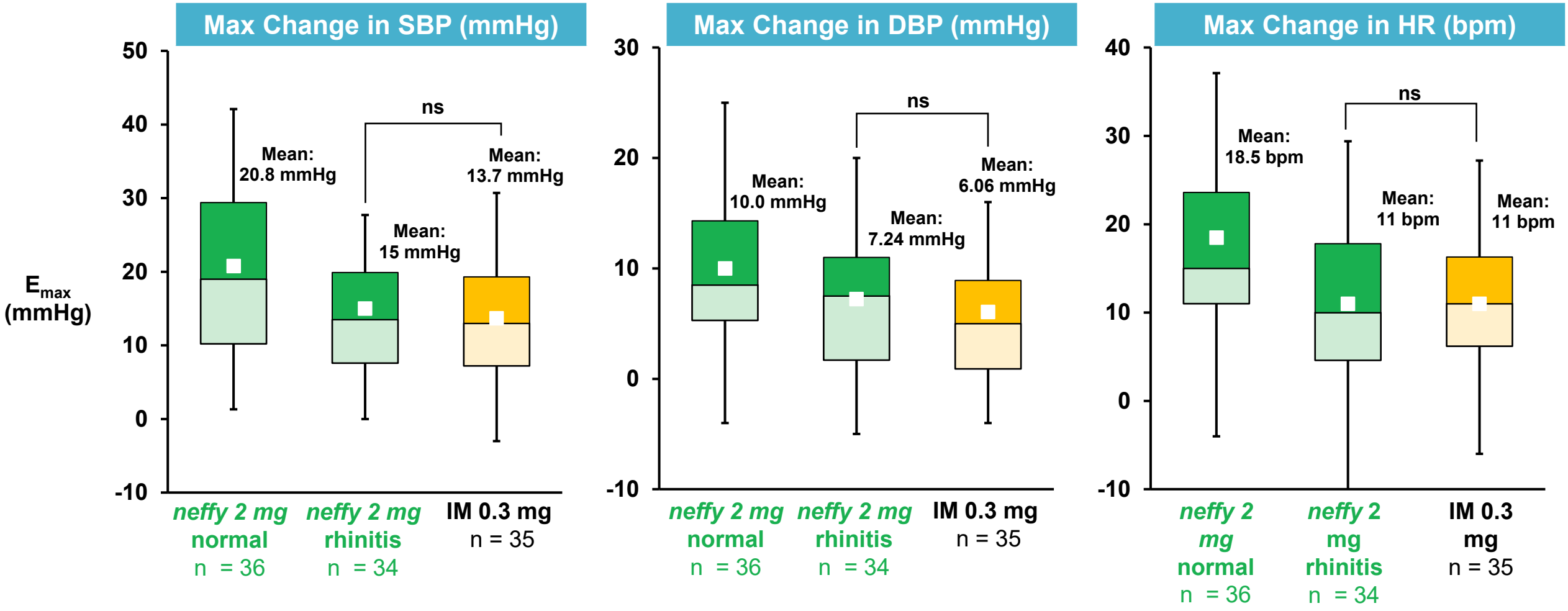
***Significant difference ($p<0.05$) between *neffy* w/ NAC rhinitis and IM; all values in tables above geometric means**

neffy with NAC Induced Rhinitis: Epinephrine Concentration at Each Time Point (EPI 16)

Treatment	N	Epinephrine Concentration at Each Time Point GeoMean (CV%)					
		2 min	4 min	6 min	10 min	15 min	20 min
***neffy* 2.0 mg rhinitis**	**34**	**144*** (91%)	**153*** (65%)	**151*** (71%)	**136** (76%)	**120** (91%)	**97** (86%)
Epinephrine IM 0.3 mg	**35**	**36** (106%)	**68** (143%)	**84** (176%)	**104** (126%)	**93** (137%)	**109** (114%

***Significant difference ($p<0.05$) between *neffy* w/ NAC rhinitis and IM; all values in tables above geometric means**

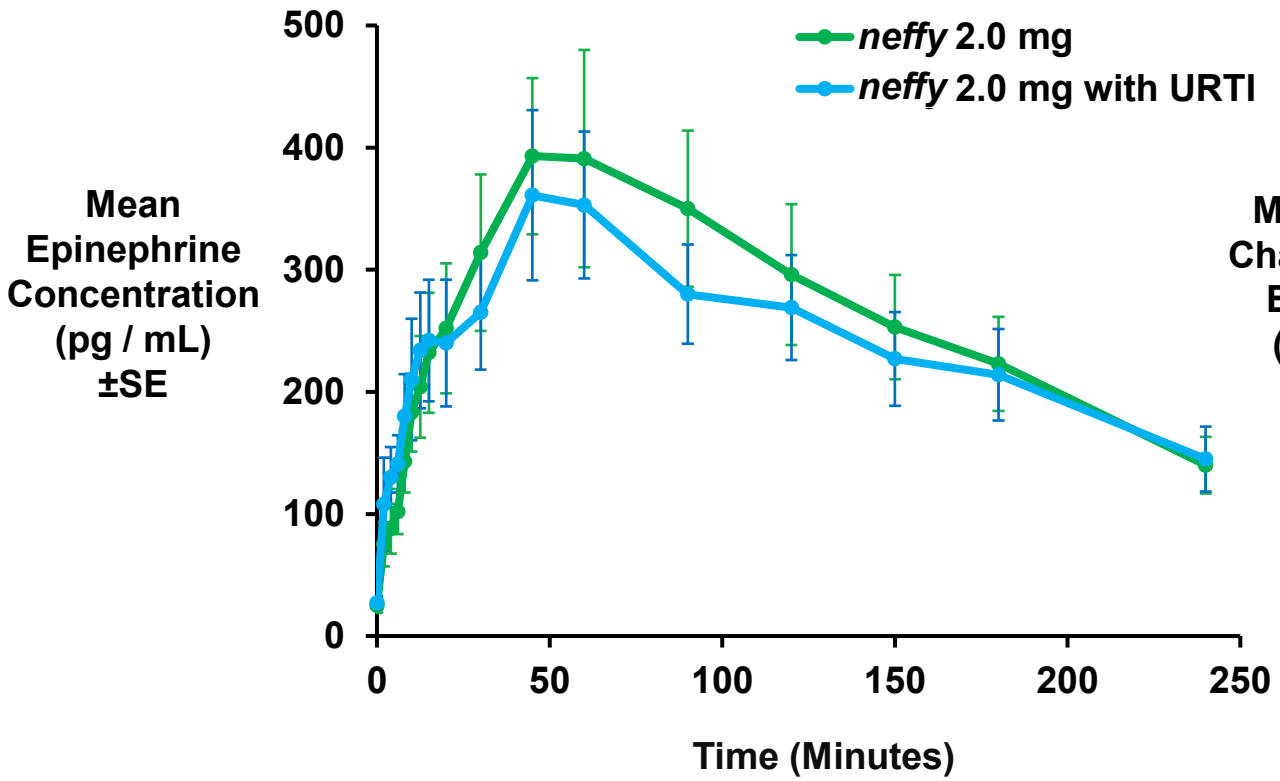
Nasal Allergen Challenge PD Results (EPI 16)



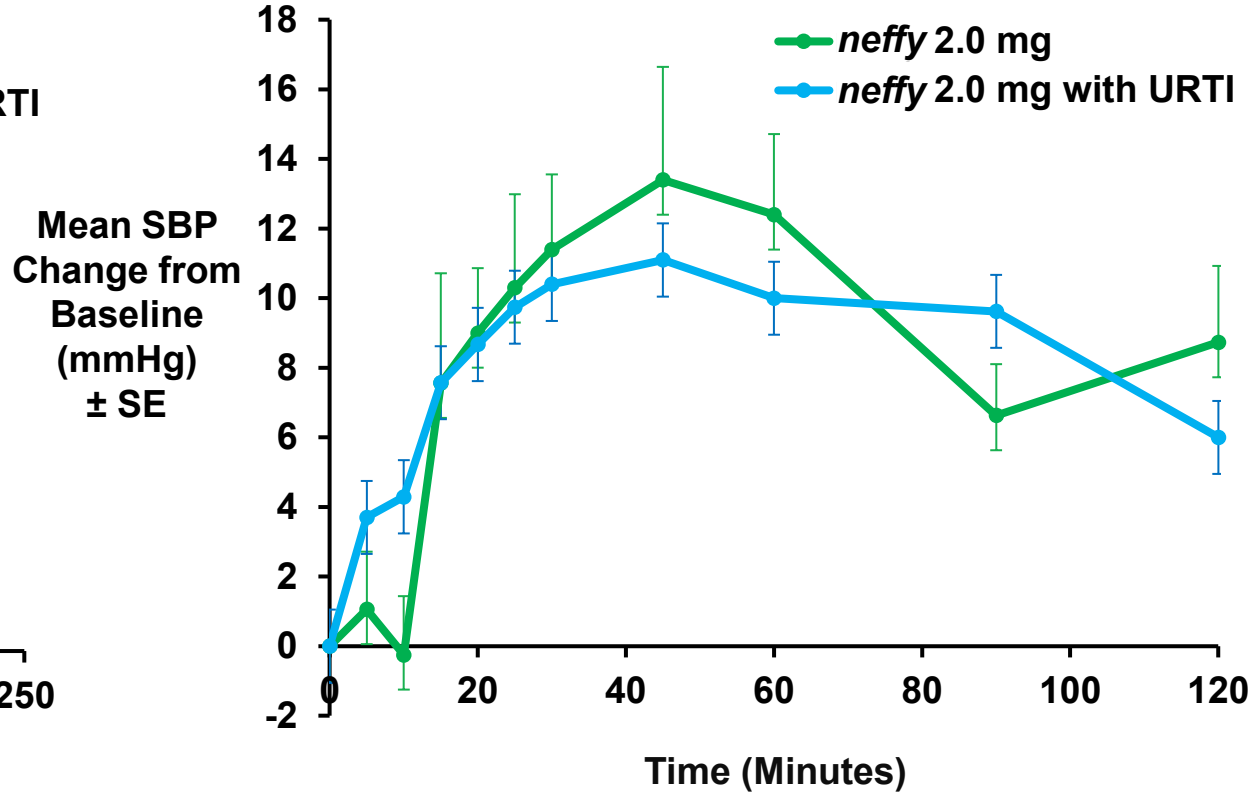
- PD response with NAC induced rhinitis lower relative to normal nasal conditions
- PD response with NAC induce rhinitis remains greater than or similar to IM injection

Upper Respiratory Tract Infections (EPI 14)

Mean Epinephrine Plasma



Mean Systolic Blood Pressure Change



N = 21 URTI / 16 Normal (returned)

neffy Safety

96% of Adverse Events Mild and Resolved Quickly

- Overall ***neffy*** safety population: N = ~ 600 subjects and > 1,120 doses
- No SAEs reported in any ARS clinical trials
- ***neffy*** 2 mg safety population: N = 134 subjects

Common TEAEs ≥ 2 Subjects (2 mg)	Frequency
Mild Nasal Discomfort	9.7%
Mild Headache	6.0%
Mild Rhinorrhea	3.0%
Mild Nausea	3.0%
Mild to Moderate Dizziness	3.0%
Mild to Moderate Vomiting	2.2%
Mild Throat Irritation	1.5%

No Meaningful Nasal Pain, Irritation, or Change in Smell

- Pain in nose, nasal irritation, and smell assessed in all studies
  - Visual Analogue Scale (VAS): mean pain scores between 5 – 8 mm out of 100 mm across studies
  - Nasal irritation: no clinically meaningful nasal irritation based on clinician assessment in every study
  - Smell: no observed impact on smell in formal assessments

Single Dose Moderate/Severe TEAEs

Treatment	Single Dose (2 mg) Adverse Events
Moderate Events	
***neffy* 2 mg** **N = 134**	• 1 subject (0.7%) • 3 events: vomiting (1), dizziness (1), heart rate decrease (1)
IM 0.3 mg **N = 274**	• 2 subjects (0.7%) • 5 events: headache (2), vomiting (1), presyncope (1), hypotension (1)
Severe Events	
***neffy* 2 mg** **N = 134**	• 1 subject (0.7%) • 2 events: syncope (1), hypotension (1)
IM 0.3 mg **N = 274**	• 2 subjects (0.7%) • 3 events: syncope (1), asthenia (1), blood pressure decrease (1)

Source: ISS for Primary Studies EPI 15, EPI 16, EPI 17 and all comparative injection data from ARS clinical trials

Consistent Safety Profile for Twice Dose (4 mg)

- 100% of ***neffy*** twice (4 mg) events mild and resolve quickly
- No SAEs reported in any ARS clinical trial
- No severe events reported in either group

Treatment	Twice Dosed Adverse Events
Moderate Events	
***neffy* 2 mg twice** • **N = 39 (R/L)** • **N = 39 (R/R)**	• No moderate events reported
IM 0.3 mg twice • **N = 70 (R/L)**	• 1 subject (1.4%) • 1 event: vomiting

Source: Integrated safety analysis (EPI 03 and EPI 15)

Pediatric Safety Observations (EPI 10 Interim Analysis)

- All TEAEs resolved with no sequela; no pain or irritation reported
- No severe or serious AEs reported

Treatment	Pediatric Adverse Events (≥ 30kg) Adverse Events
Mild Events	
***neffy* 2 mg** **N = 21**	• 12 subjects (57.1%) • 32 events: intranasal paraesthesia (4), nasal discomfort (3), rhinorrhoea (3), sneezing (2), epistaxis (2), rhinalgia (2), fatigue (2), feeling jittery (2), paraesthesia (2), nasal congestion, oropharyngeal pain, pharyngeal paraesthesia, throat irritation, hypoaesthesia, palpitations, lacrimation increased, heart rate increased, nervousness, vein rupture (1 each)
Moderate Events	
***neffy* 2 mg** **N = 21**	• 1 subject (4.8%) • 2 events: nasal discomfort, sneezing

neffy Safety Conclusions

- Low frequency of AEs in adults and pediatric subjects with ***neffy*** 2 mg dosed once and twice
- AEs almost always mild and resolve quickly with no sequela
- No meaningful nasal pain or irritation
- No risk of needle-related injuries to patient or caregiver, including potential injection into a blood vessel
- Increase in SBP and HR within normal physiologic range

Clinical Perspective and Conclusion

Dr. John Oppenheimer, MD
Clinical Prof. of Medicine
UMDNJ – Rutgers University
Director, Clinical Research Pulmonary & Allergy

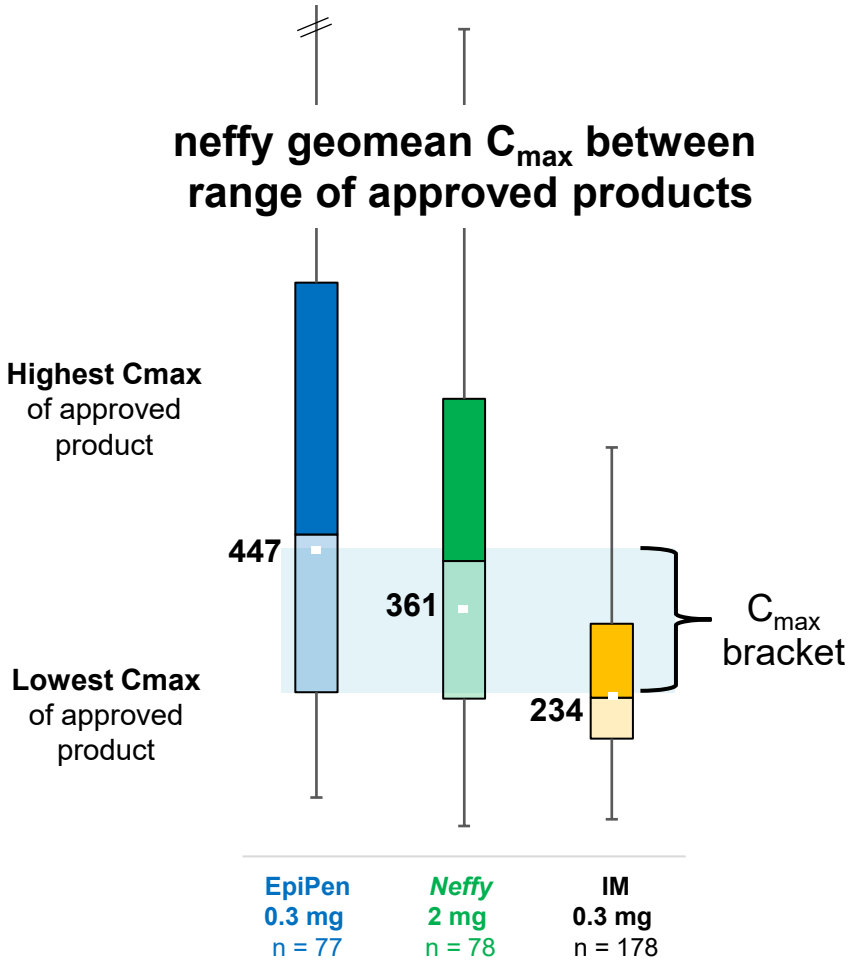
Unmet Medical Need - Injection Only Current Option

- Primary challenges for physicians, patients and caregivers with currently available injection products
  - Needle-phobia
  - Cumbersome
  - Difficult to use
  - Fear of injury
- Hesitation to dose proven to result in worse clinical outcomes
- Patients who will benefit most are those who will not accept or properly use current autoinjector options

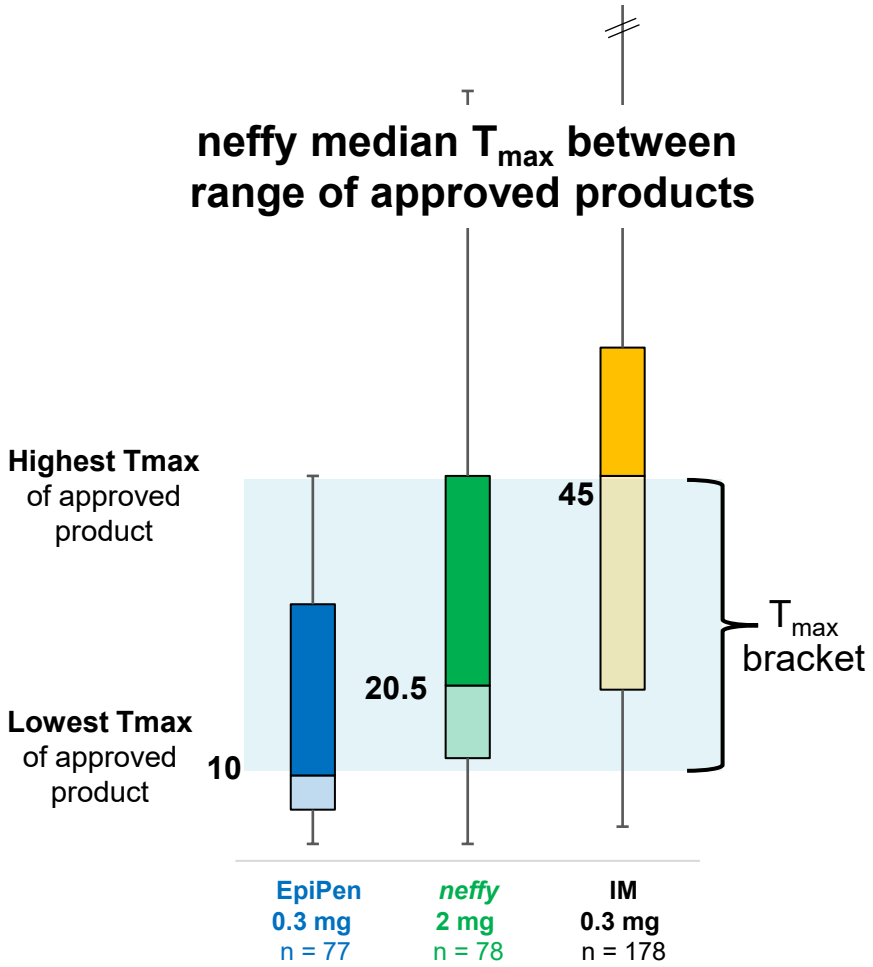
neffy provides a discrete, needle-free, easy to carry, and easy to use epinephrine product people will use more quickly when needed

neffy PK Results Support Safe and Effective Exposures Within Range of IM Epinephrine and EpiPen

Plasma Epinephrine C_{max} (pg/mL)



Median T_{max} (minutes)



AUCs

Geomean early partial AUCs bracketed by approved products

Treatment	pAUC (0-20)	pAUC (0-45)
EpiPen 0.3 mg	4,240 (95)	10,200 (64)
neffy 2 mg	**2,640 (100)**	**8,140 (101)**
IM 0.3 mg	1,520 (97)	5,260 (68)

Overall geomean AUC(0-t) bracketed by approved products

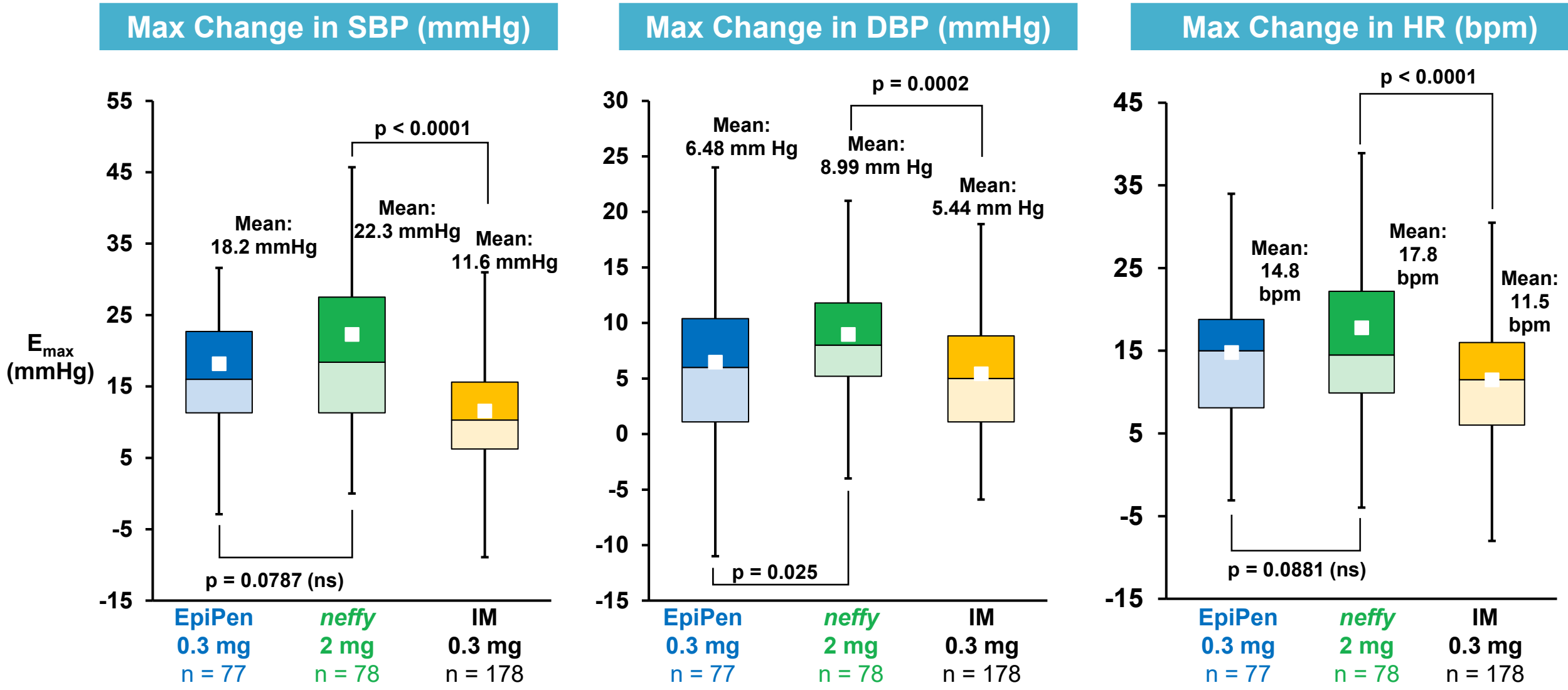
Treatment	AUC_{0-t}
IM 0.5 mg	41,300 (35)
neffy 2 mg	**32,600 (81)**
IM 0.3 mg	26,100 (37)

% CV shown in parentheses in tables above

Totality of PK Data Supports *neffy* Meets Bracket

Parameter	Geometric Mean									
	EPI 15			EPI 17			EPI 16			
	neffy 2 mg N=42	IM 0.3 mg N=42	p-value	neffy 2 mg N=42	IM 0.3 mg N=42	p-value	*neffy* 2 mg N=36	IM 0.3 mg N=35	p-value	Bracket (≧IM) Y / N
C_{max}(pg/mL)	340	283	0.2044	332	274	0.1333	386	216	<0.0001	Y
T_{max}(min)	30	45	0.1074	30	45	0.3284	20	45	0.0216	Y
$AUC_{0\text{-}10min}$ (pg*min/mL)	704	879	0.1775	784	550	0.0208	738	647	0.5064	Y
$AUC_{0\text{-}20min}$ (pg*min/mL)	2,590	2,030	0.0891	2,314	1,549	0.0127	2,700	1,550	0.0020	Y
$AUC_{0\text{-}30min}$ (pg*min/mL)	4,880	3,420	0.0095	4,757	3,095	0.0045	5,120	2,740	<0.0001	Y
$AUC_{0\text{-}60min}$ (pg*min/mL)	10,900	9,220	0.1765	12,033	8,585	0.0155	10,700	7,080	0.0024	Y

neffy PD Results: Emax Similar to EpiPen (Single Dose)



E_{max} = Maximum effect

neffy Safety Results: Positive Safety Profile

- Mild side effects with ***neffy*** 2 mg and similar to IM injection
- Avoids needle related injuries to patients and caregivers
  - No potential for IV bolus injection
  - No potential for accidental injection into extremities
- No meaningful pain or irritation
- No impact on sense of smell
- Maximum change in SBP and HR comparable to or less than EpiPen with once and twice dosing and within normal physiologic ranges

Overall Conclusions: Clinician Perspective – Benefit / Risk

- ***neffy*** PK and PD within efficacious range of current injection products
  - PK is within bracket of exposures for injection products, even for first 10 min.
  - PD response generally better than injection and is the important consideration for clinical efficacy
  - Second dose of epinephrine provides proportional increase in absorption
  - Pediatric data in > 80 allergy patients demonstrates utility in children
- Safety data appears favorable and will naturally remove risks of needle related injuries or accidental injections
- ***neffy's*** needle-free device offers easier carriage and has potential to overcome current challenges with existing autoinjectors

NEEDLE – FREE ALTERNATIVE EPINEPHRINE NASAL SPRAY

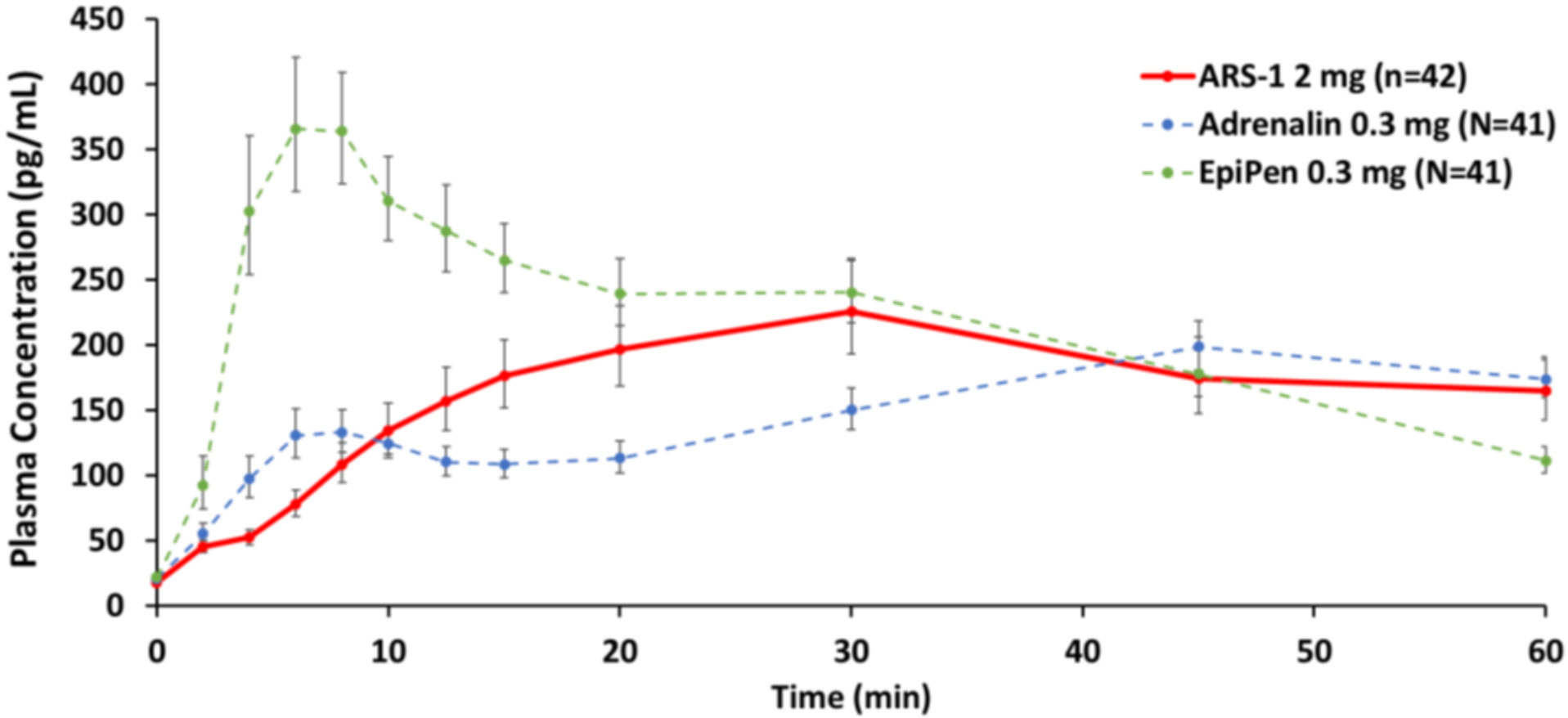
for Type I Allergic Reactions

11 May 2023

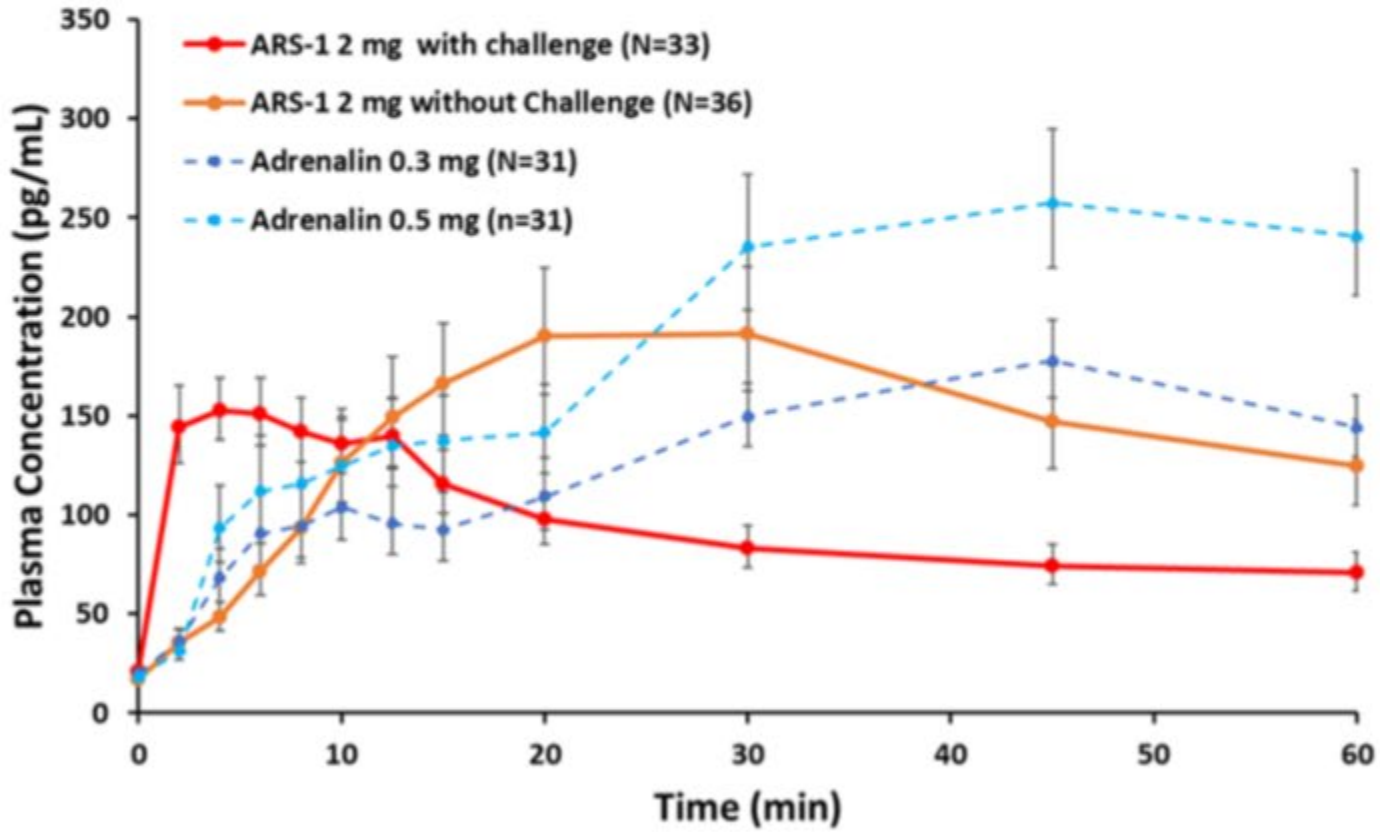
ARS Pharmaceuticals, Inc.

Pulmonary-Allergy Drug Advisory Committee

FDA Figure 1. Epinephrine Geometric Concentration-Time Profile Following a Single Dose of ARS-1 (2 mg) vs. a Single Dose of Intramuscular Injection Using



FDA Figure 2. Epinephrine Geometric Mean Plasma Concentration-Time Profiles in Subjects With Allergic Rhinitis



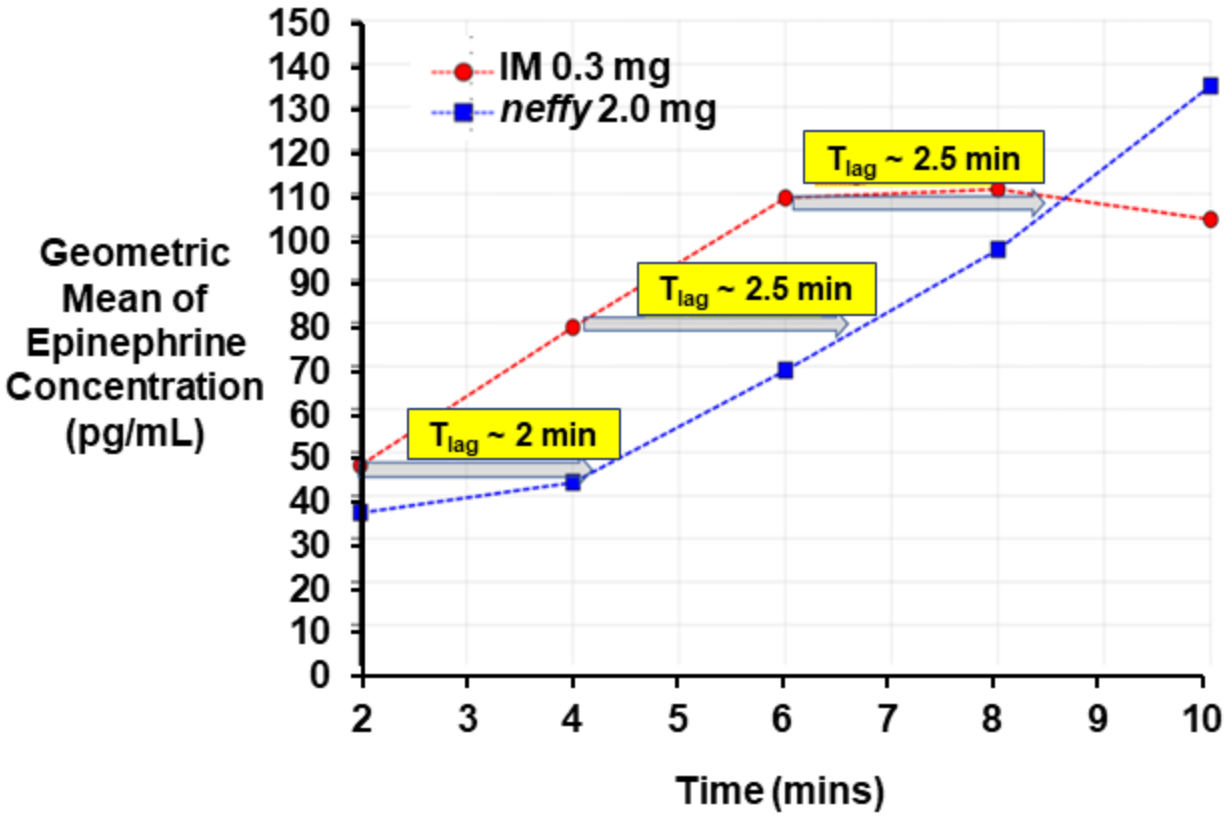
EPI-15 PK Bracketing by Statistical Analysis (Exposures ≥ IM/SC for Efficacy, < EpiPen for Safety)

Parameter	Geometric Mean (CV%) Arithmetic Mean (CV%) ARS-1 2 mg N=42	Adrenalin 0.3 mg IM N=42	EpiPen 0.3 mg IM N=42	p-value (ANOVA)[1] ARS-1 vs Adrenalin	ARS-1 vs EpiPen	Bracketed by Statistics (Y/N)
C_{max}(pg/mL)	340 (114%)	283 (63%)	604 (79%)	0.2044	0.0001	Y
T_{max}(min)	30	45	7.5	0.1074	< 0.0001	Y
$AUC_{0\text{-}10min}$ (pg*min/mL)	704 (92%) 976 (106%)	879 (120%) 1,330 (101%)	2,770 (115%) 3,870 (75%)	0.1775	< 0.0001	Y
$AUC_{0\text{-}20min}$ (pg*min/mL)	2,590 (102%) 3,600 (89%)	2,030 (89%) 2,670 (79%)	5,820 (83%) 7,260 (62%)	0.0891	< 0.0001	Y
$AUC_{0\text{-}30min}$ (pg*min/mL)	4,880 (109%) 6,840 (85%)	3,420 (78%) 4,260 (69%)	8,530 (70%) 10,100 (55%)	0.0095	< 0.0001	Y
$AUC_{0\text{-}60min}$ (pg*min/mL)	10,900 (116%) 15,700 (83%)	9,220 (59%) 7,340 (61%)	14,800 (57%) 13,900 (46%)	0.1765	0.0181	Y

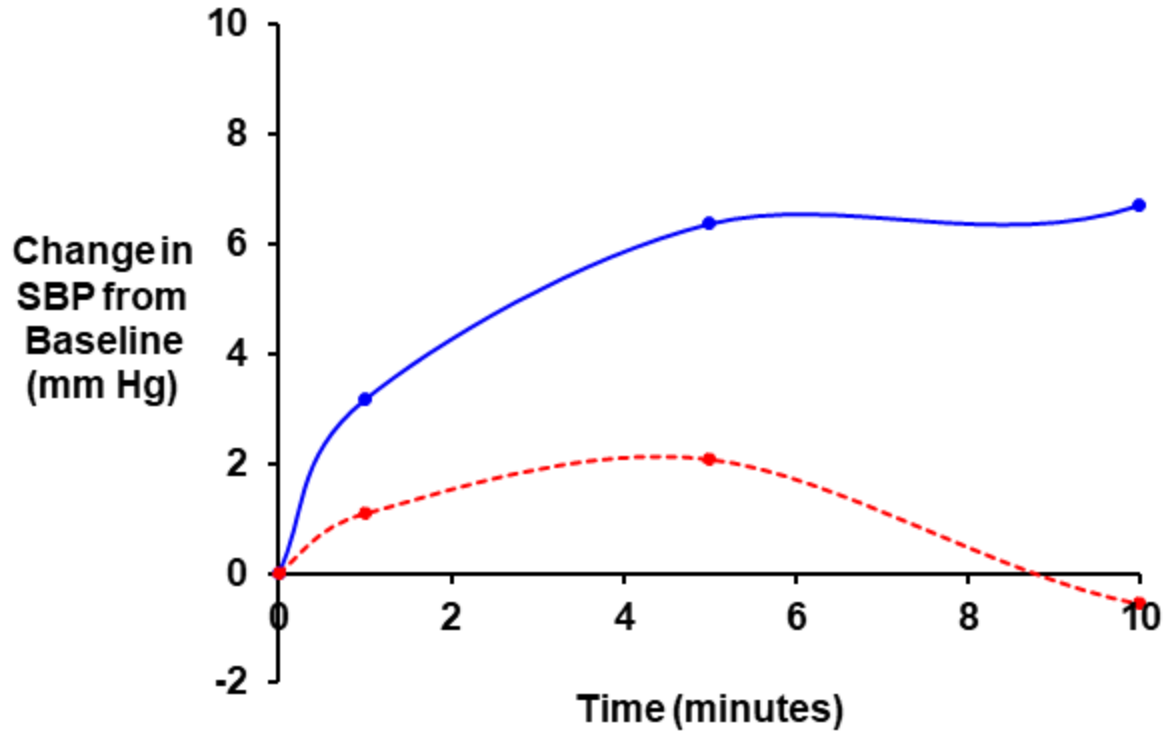
1. Except for tmax, which is Wilcoxin signed ranked test

First 10 Minutes Exposure and PD Response: IM vs *neffy* (EPI-15)

Exposures in First 10 min



PD Response in First 10 min



EPI 16 Designed to Induce Nasal Congestion and Rhinitis
(Antigen Directly Sprayed onto Nasal Mucosa)

Randomized, four-treatment crossover study in 36 allergic rhinitis patients (2.0 mg neffy normal, 2.0 mg neffy rhinitis, 0.3 mg IM and 0.5 mg IM)

Enrollment Criteria

- Assess for seasonal allergic rhinitis to purified tree or grass allergens
- Identify allergen dose required through escalation until Positive Reaction Criteria met

Positive Reaction Criteria

Total Nasal Symptom Score (TNSS) of ≥ 5 out of 12
- **Congestion**
- **Running Nose**
- Itching
- Sneezing

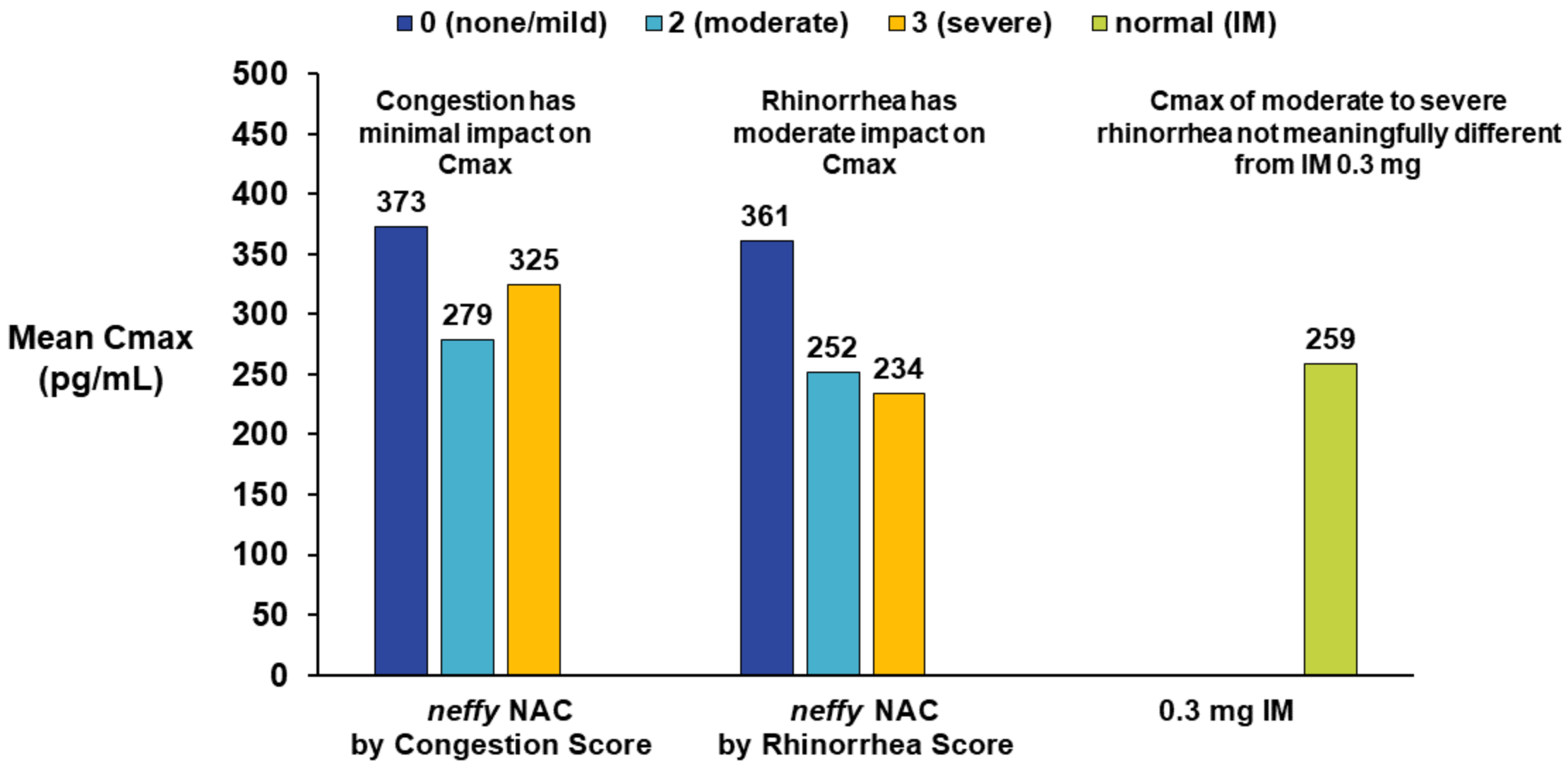
Each component reported from: 0 (none) to 3 (severe)

Congestion component score of ≥ 2 out of 3 (at least moderate)

Induction of Positive Reaction

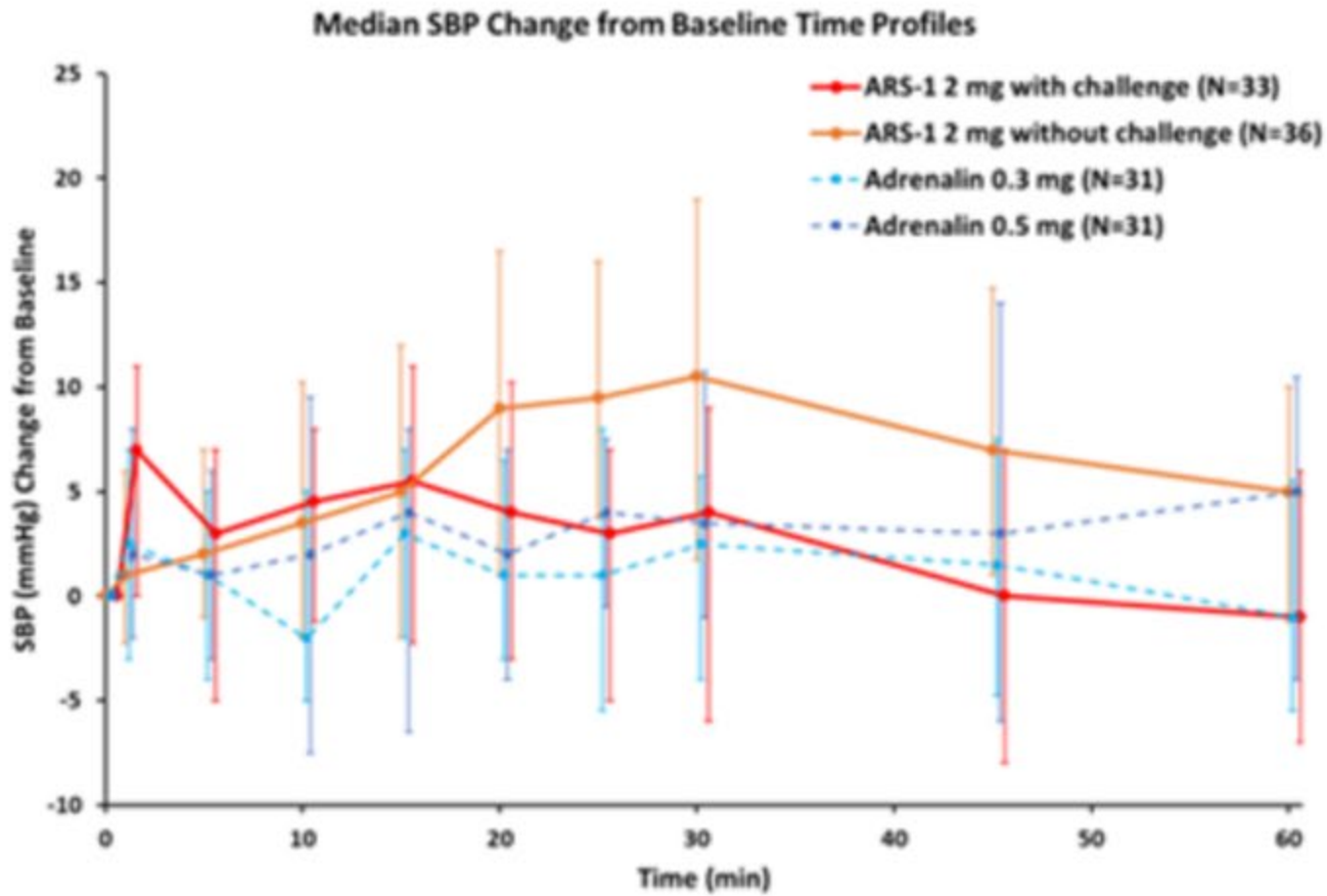
- Challenge **patient sitting upright** with antigen by spraying directly into the nose
- If Positive Reaction not achieved within 15 minutes, second challenge with 400% increase in antigen dose.
- Following Positive Reaction, **immediately dose 2.0 mg *neffy* without delay and allowing recovery**, and measure PK and PD

C_{max} vs. Congestion or Rhinorrhea (EPI-16)

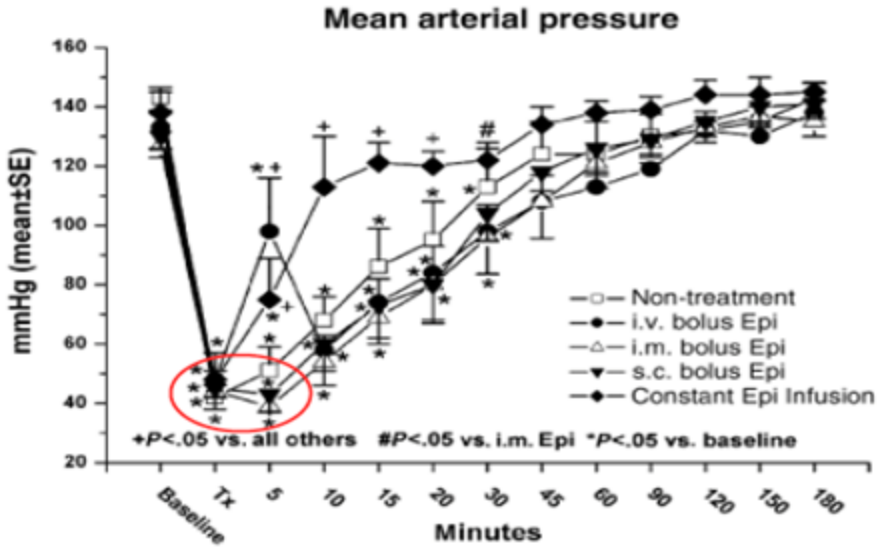


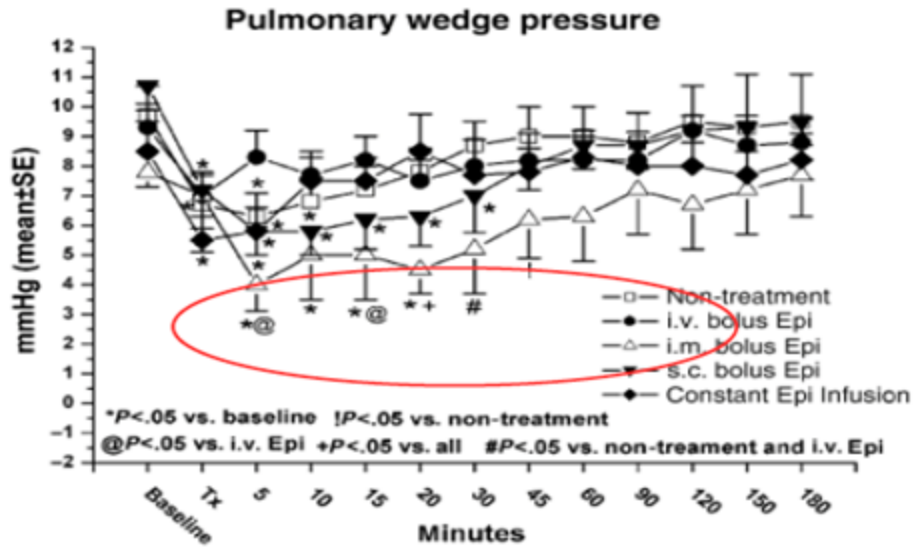
FDA Figure 12 Median PD Response Based on SBP Demonstrates Sustained Effect Through 60 Minutes

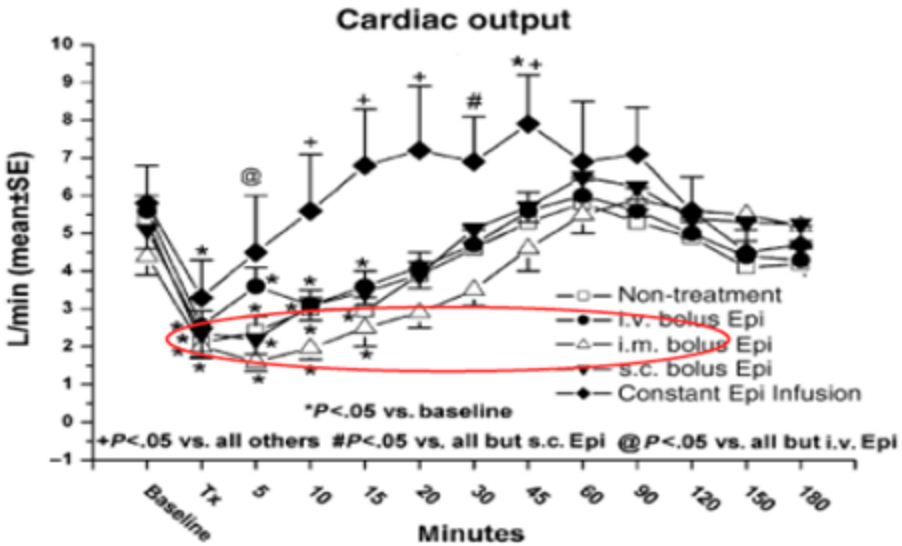
Median SBP change from baseline

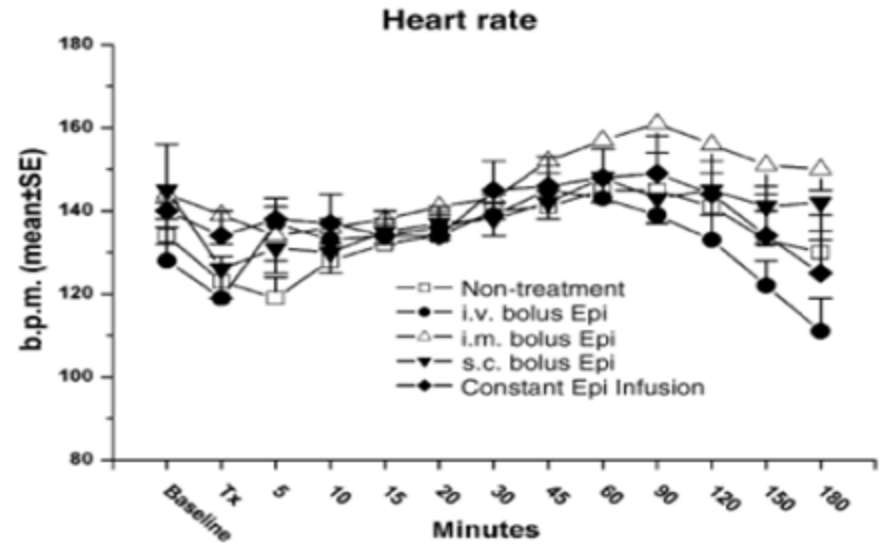


Dog Anaphylaxis Model: IV Bolus, IV Infusion, IM, SC, Control



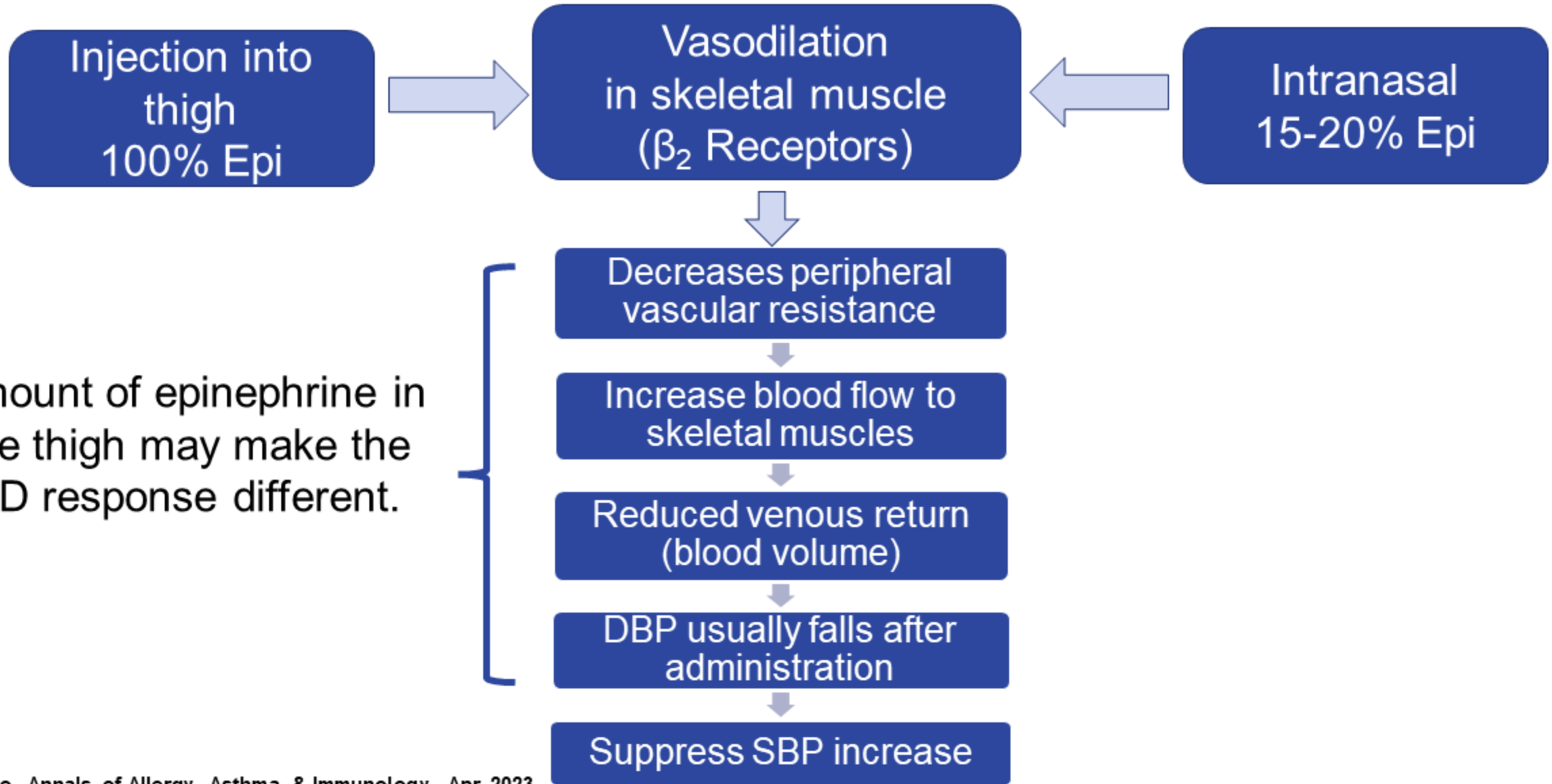






Mink 2004

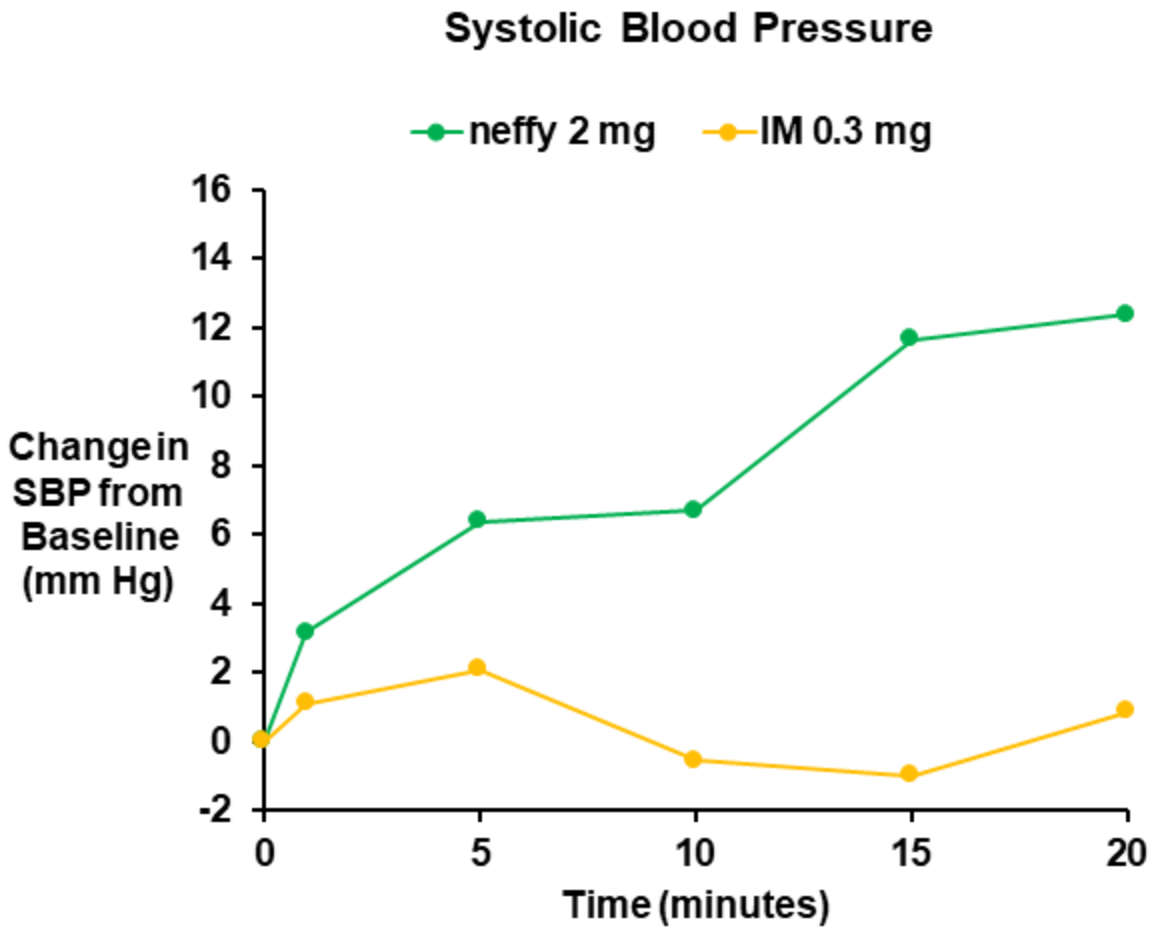
Differential Activation of β2 Receptors in Skeletal Muscles Promotes Vasodilation/Blood Redistribution, Changing PD

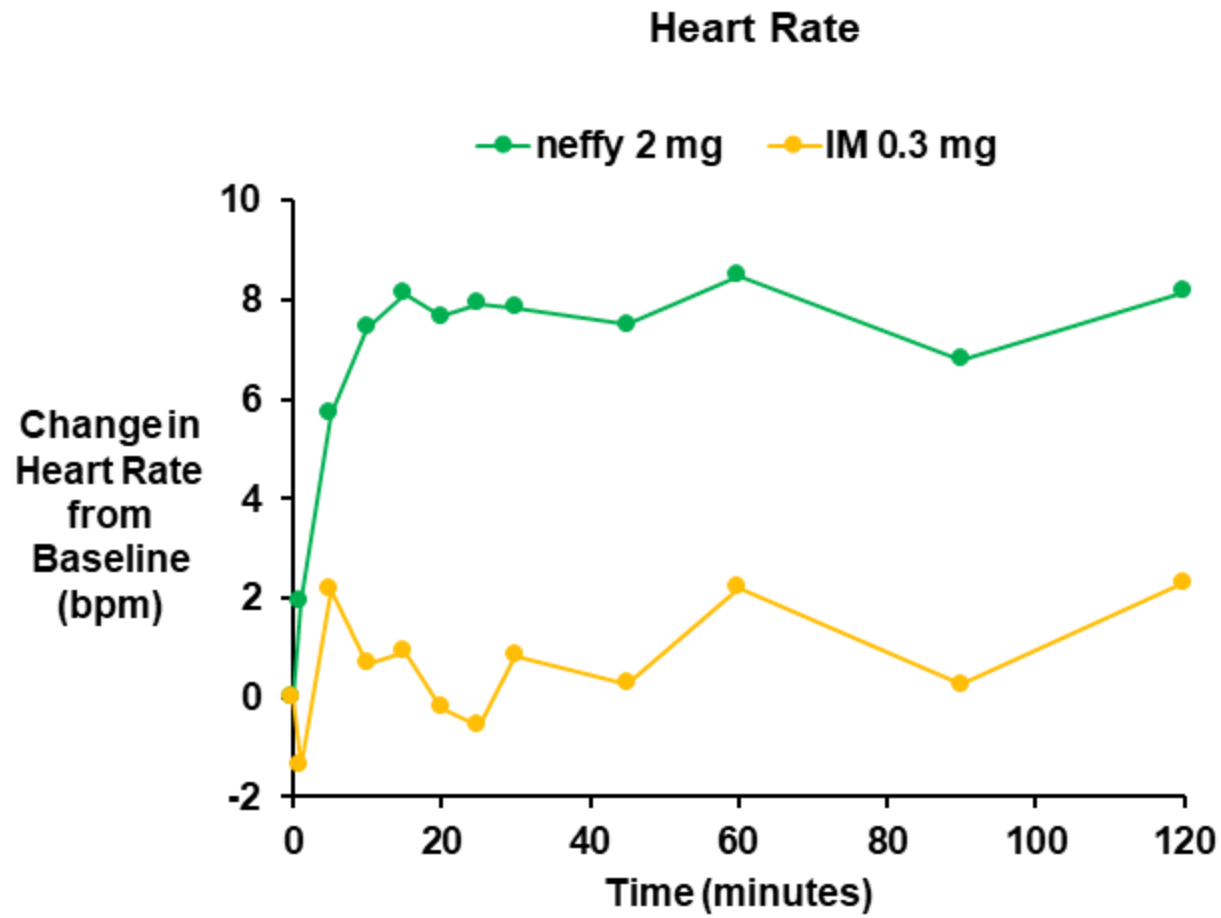


Amount of epinephrine in the thigh may make the PD response different.

Tanimoto. Annals of Allergy, Asthma & Immunology. Apr 2023

Pharmacodynamic Responses Observed (First 20 Minutes) (EPI-15)

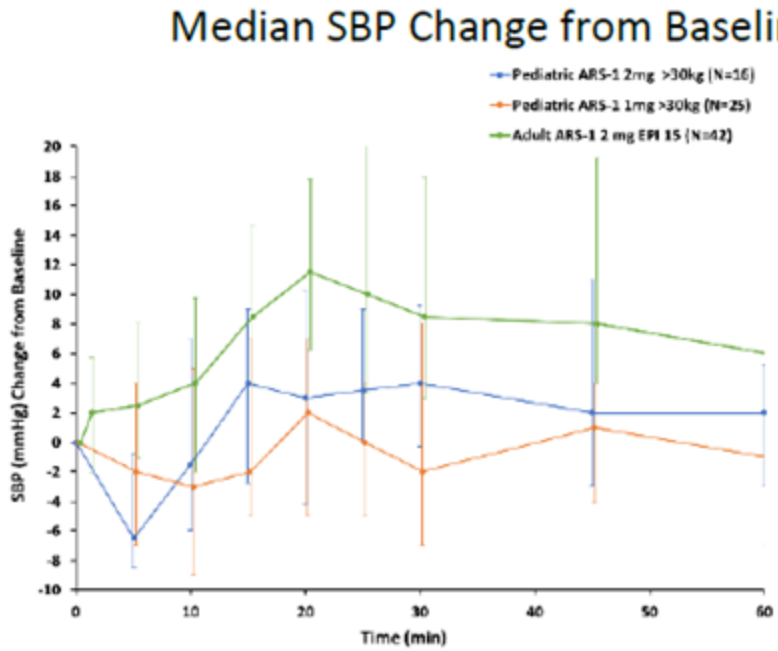


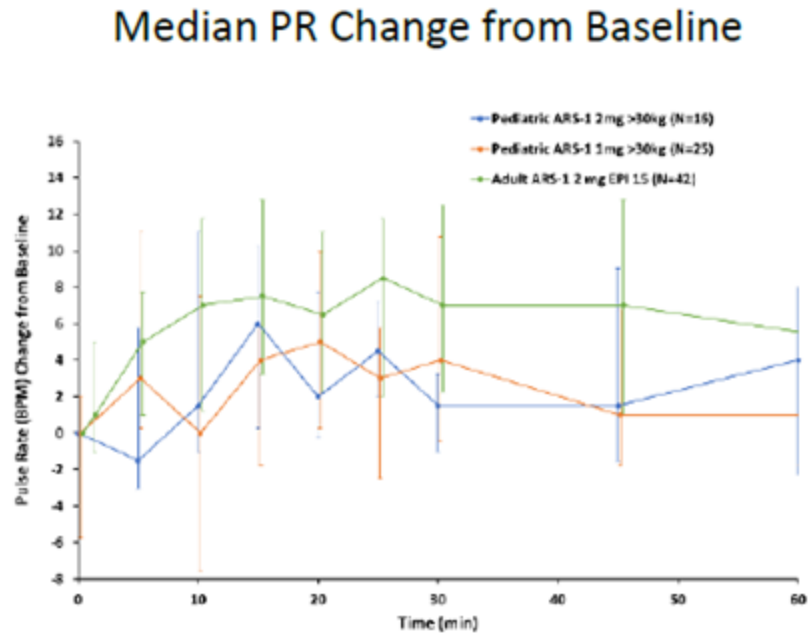


Demographics of Pediatric Study (EPI 10)

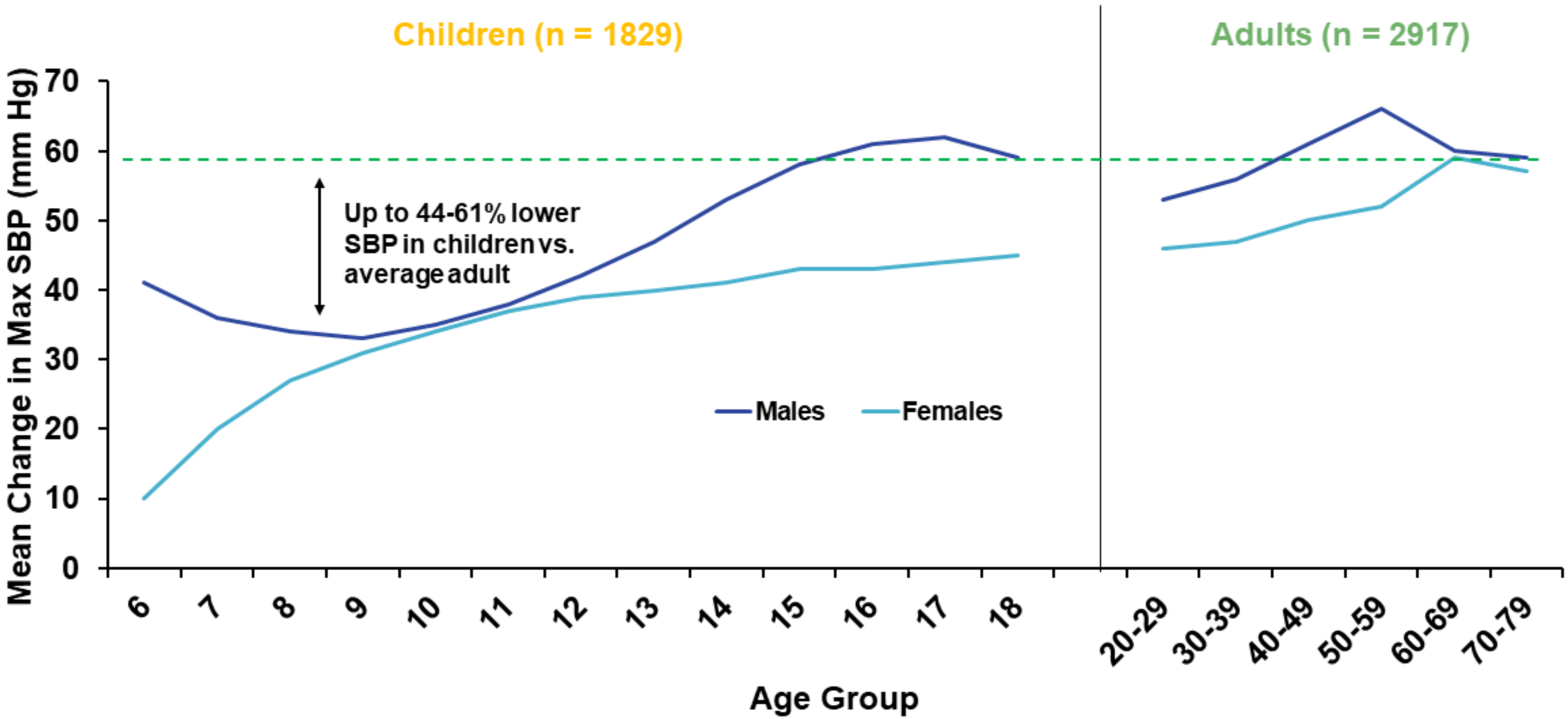
	neffy 2.0 mg IN N = 21
Age (Years), mean (SD)	**14.1** (2.4)
Median, [min, max]	**14,** [8, 17]
Sex, n (%)	
Male	**12 (57%)**
Female	**9 (43%)**
Race, n (%)	
White	**15 (71%)**
Black or African American	**4 (19%)**
Asian	**2 (10%)**
Other	**0**
Ethnicity	
Hispanic or Latino	**0**
Not Hispanic or Latino	**21 (100%)**
Weight (kg), mean (SD)	**54.1** (13.5)
Median, [min, max]	**54,** [31, 86]

FDA Figure 18. Median PD Responses Following a Single Dose of ARS-1 (1 mg or 2 mg) in Pediatric Subjects ≥ 30 kg and a Single Dose of ARS-1 (2 mg) in Adult Healthy Subjects From Study EPI 15





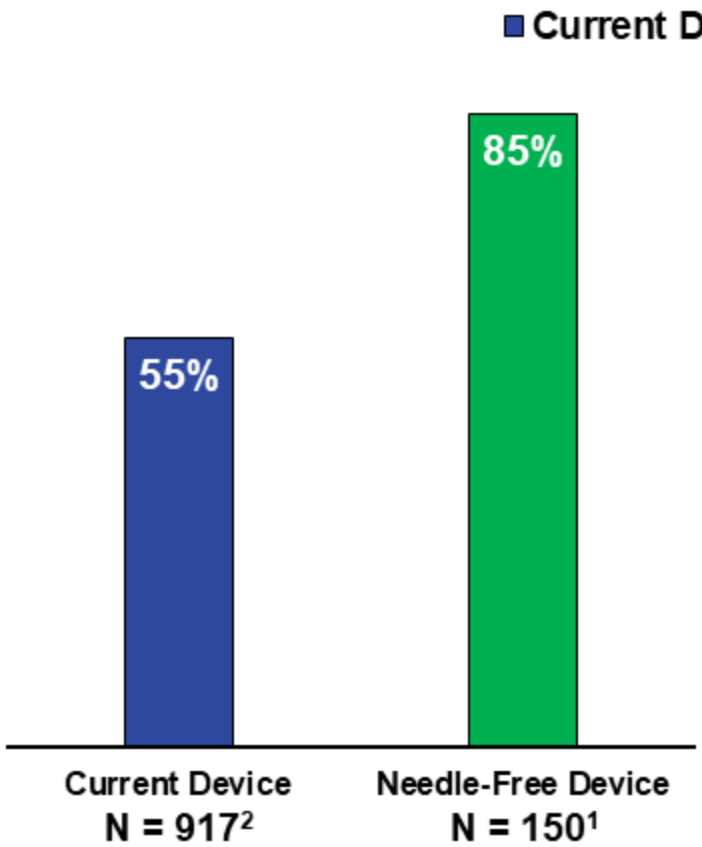
Hemodynamic Response (Systolic Blood Pressure) During Normal Exercise is Lower in Children than Adults



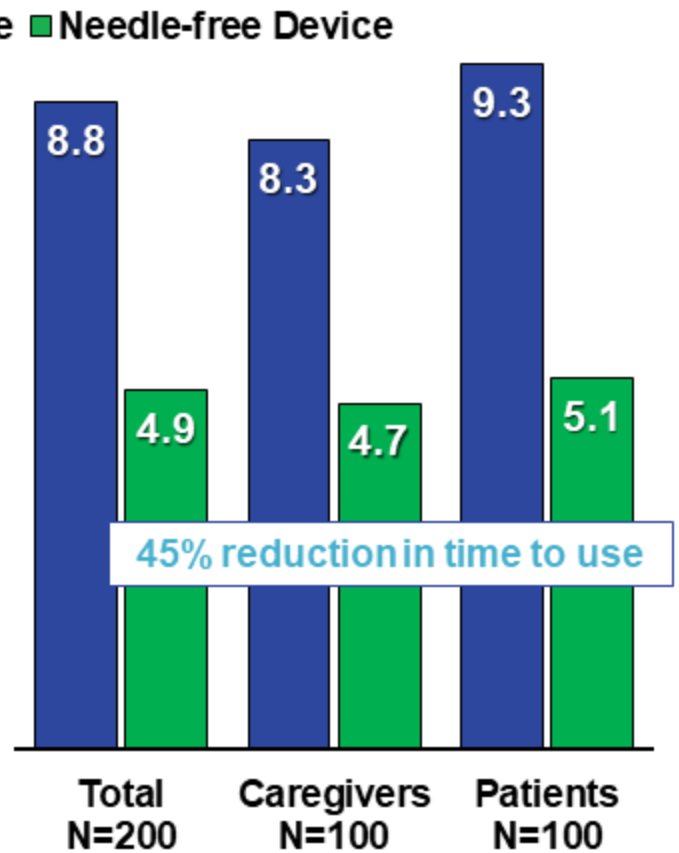
1. Burstein 2021 2. Sabbahi 2018

neffy Can Address Unmet Needs of Allergy Patients

% of Time Carrying at least One Epinephrine Device[1,2]



Average Time (minutes) from Symptom Start to Device Use[3]



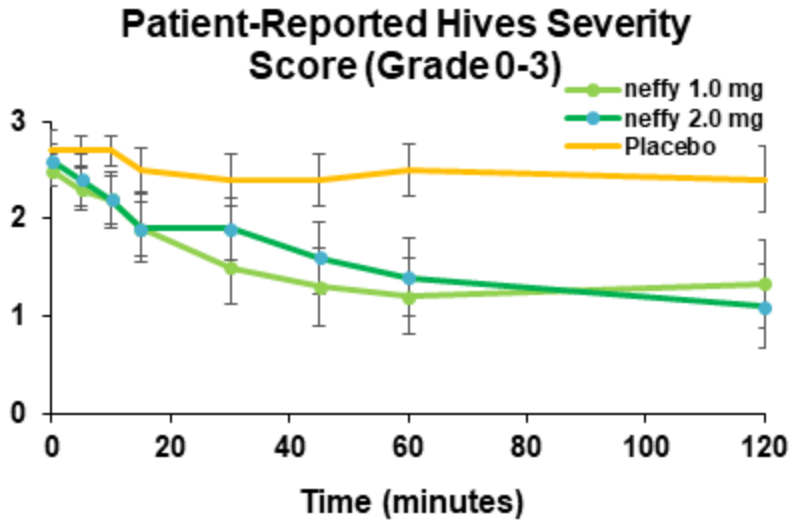
Benefit of needle-free alternative to major unmet medical needs

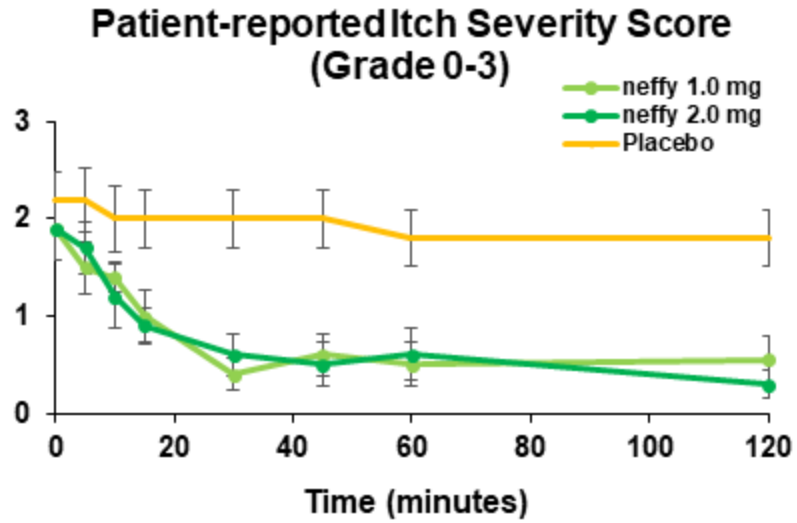
- More allergy patients and caregivers will carry *neffy* vs current needle-bearing options
- Patients will dose epinephrine more rapidly with a needle-free device

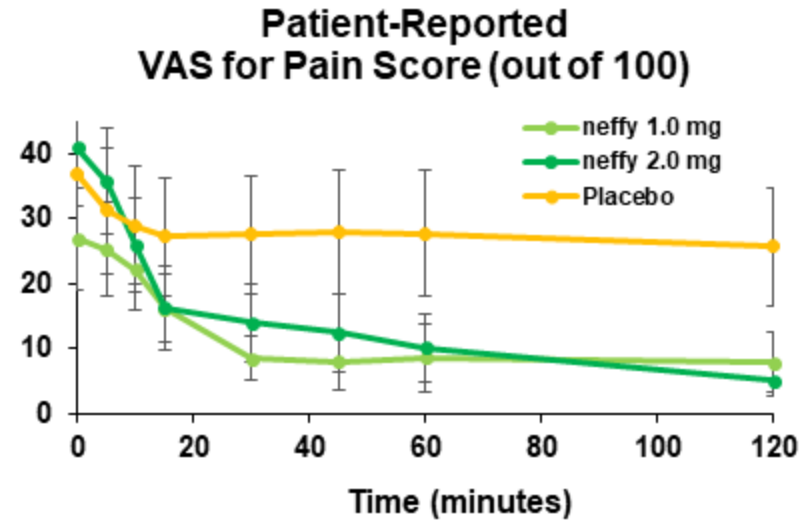
1. ARS patient survey data, 2. Warren 2018, 3. Rooney 2022

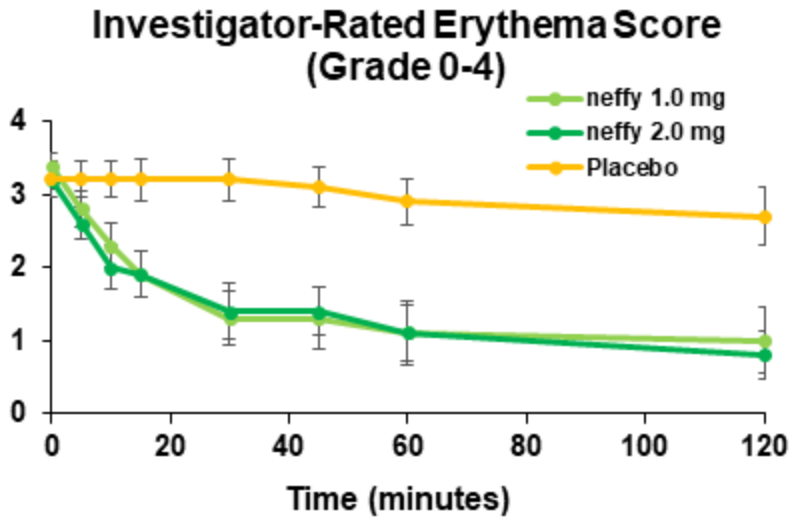
Preliminary Data (n=10): Patient and Physician Reported with ARS-1 2 and 1 mg Doses (EPI U01)

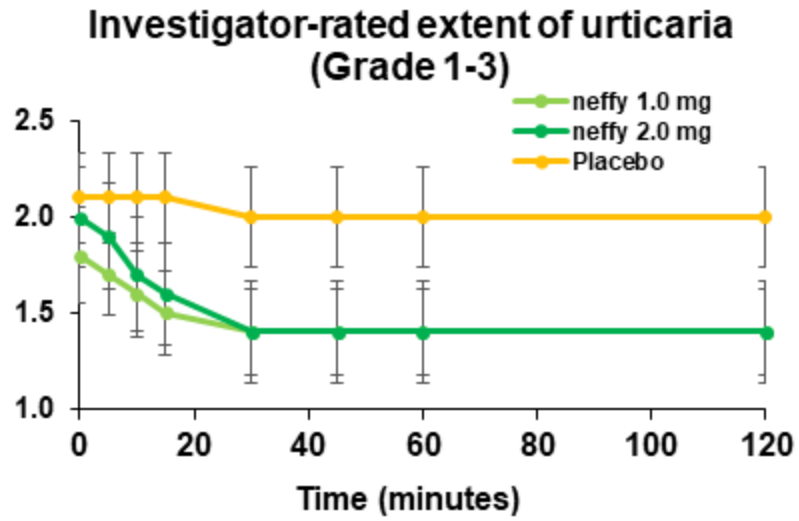
- Rapid response starting immediately after administration for patient and physician assessments.



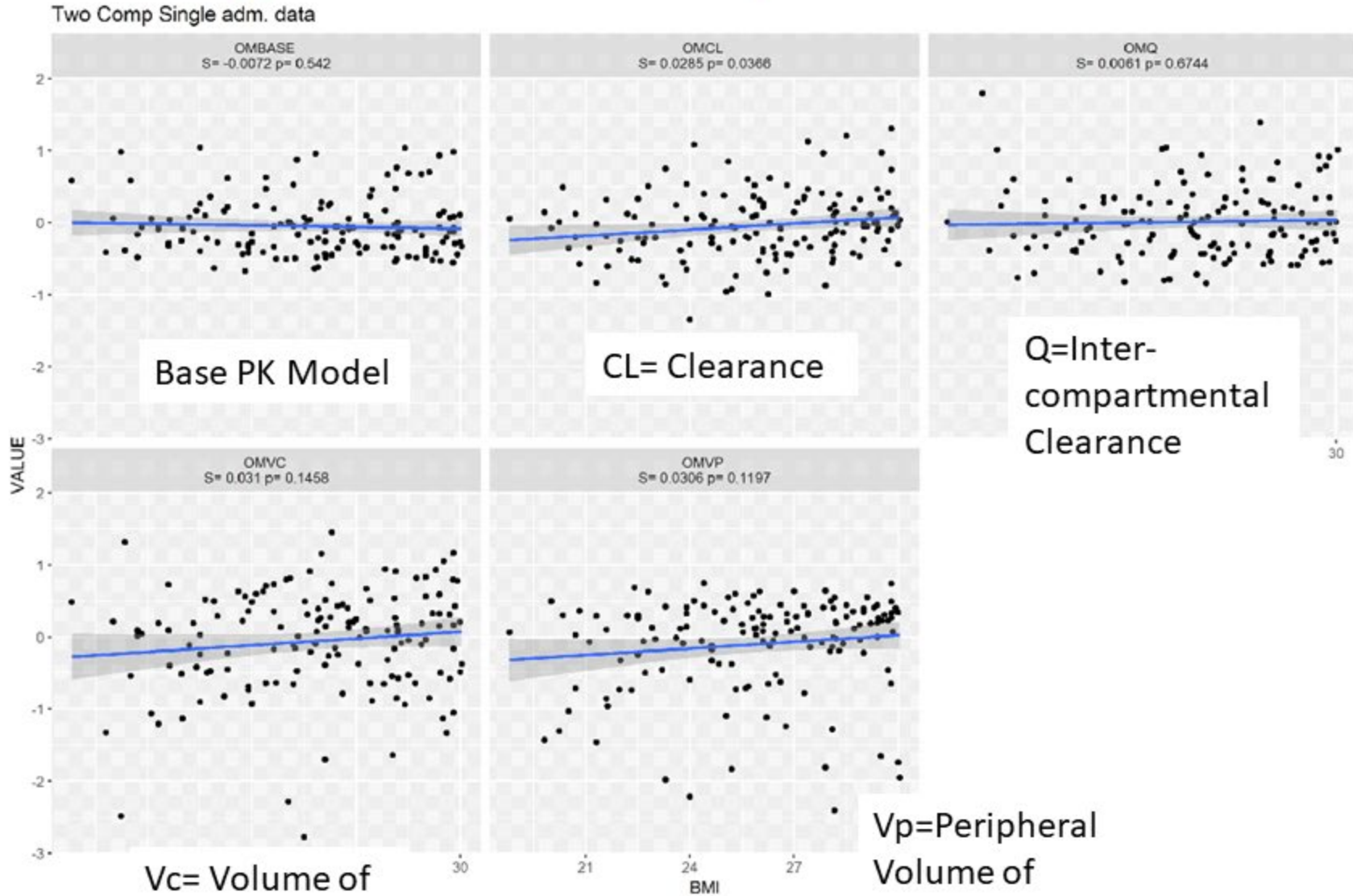






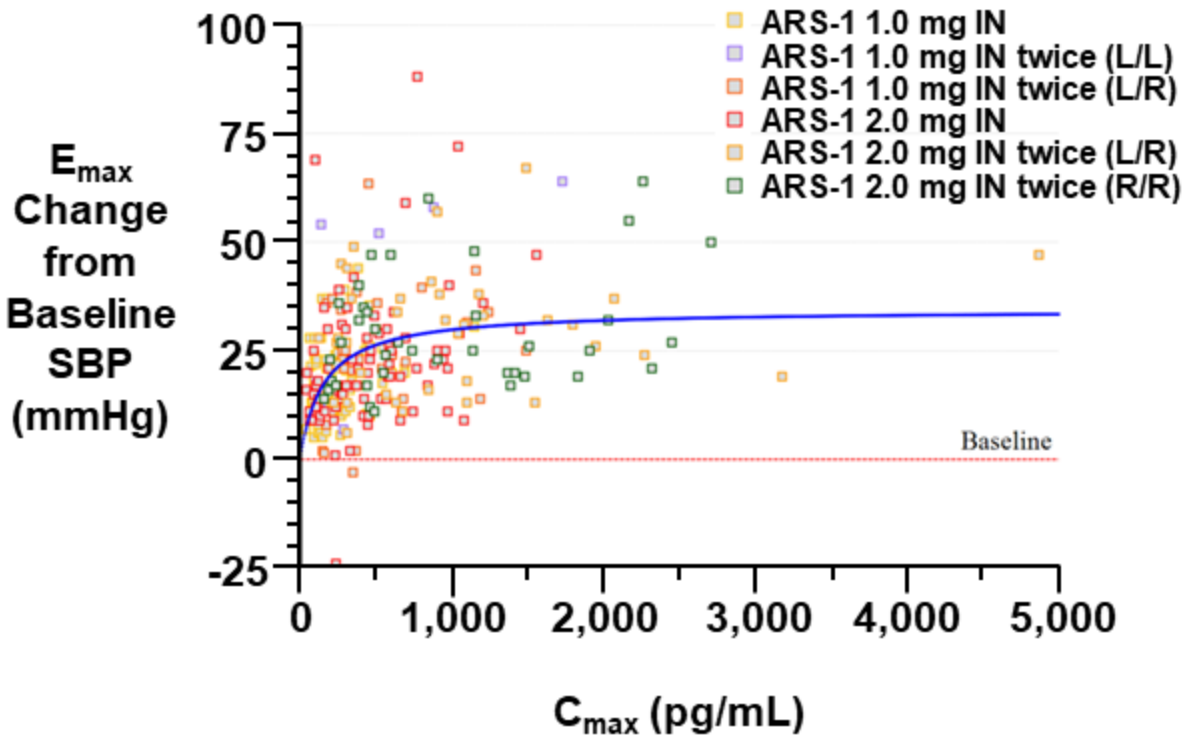


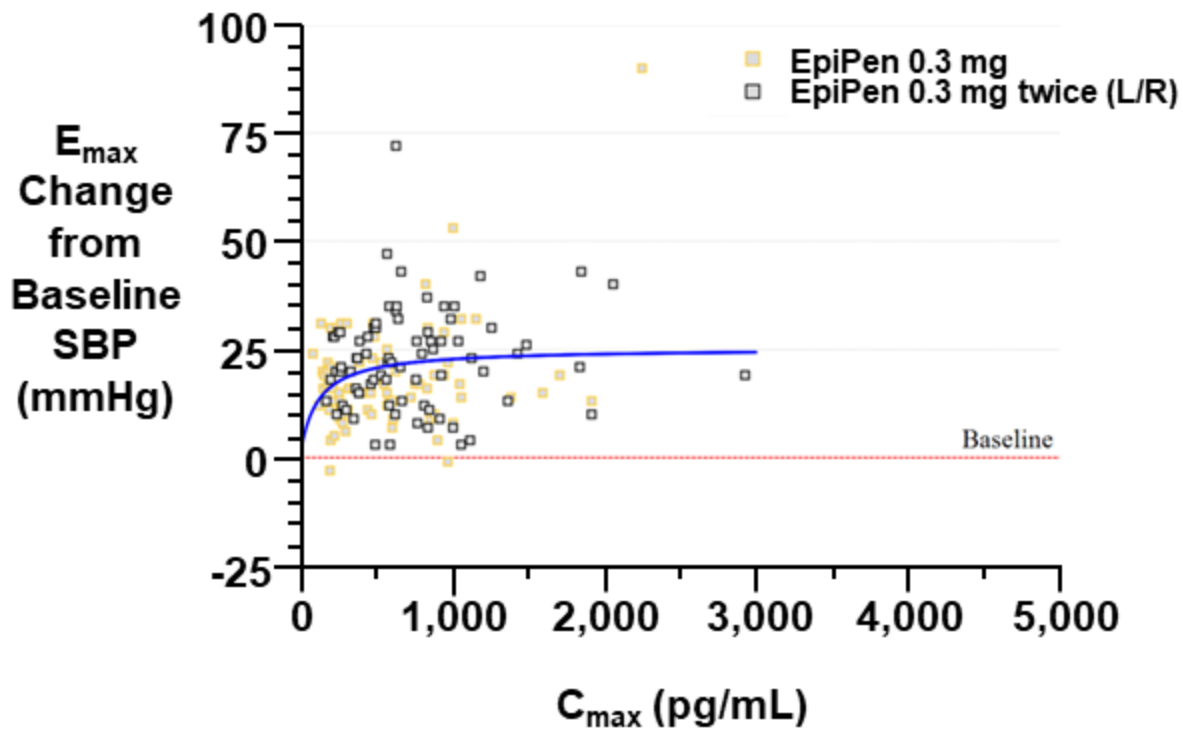
neffy No Meaningful Relationship Between BMI and PK



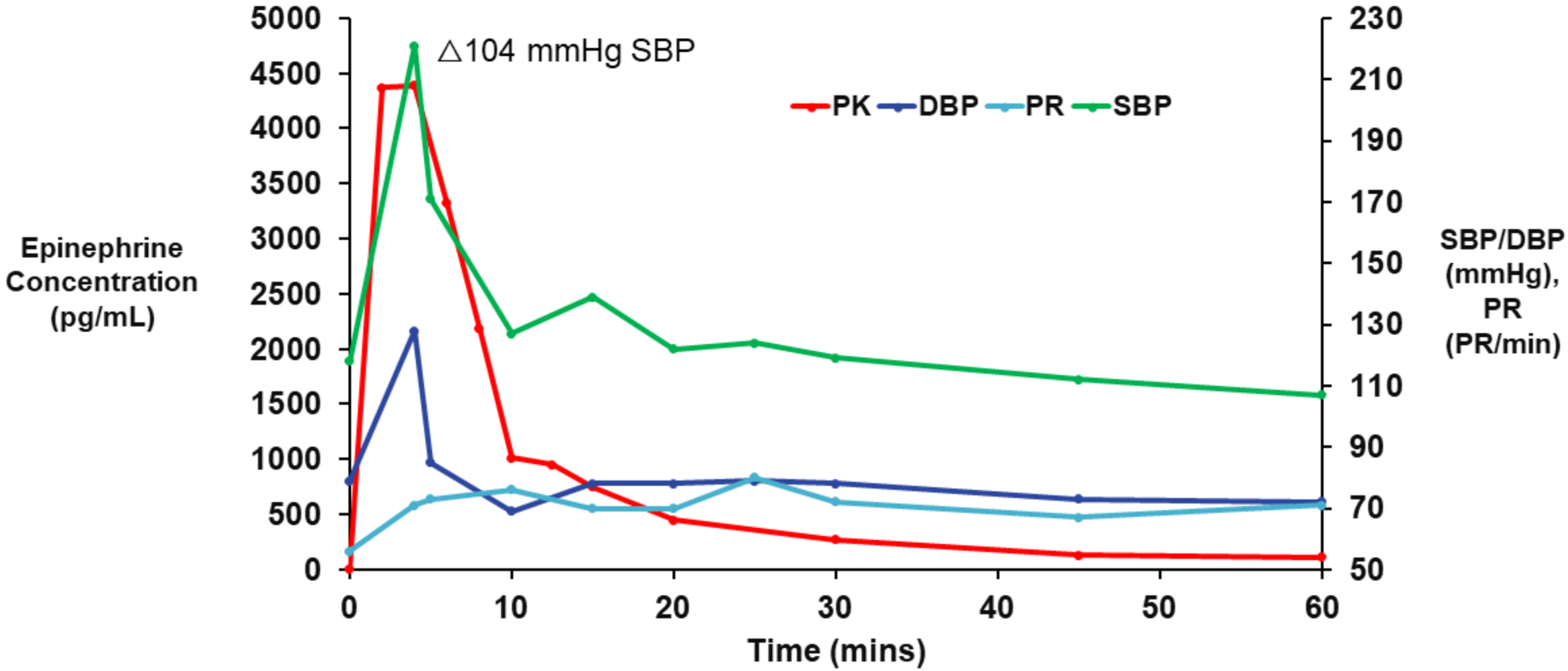
All data relates to *neffy*

C_{max} vs. E_{max} – SBP Ceiling Effect





Single Patient Case Study: Example of Intra-blood Vessel Administration



Ebisawa 2022