neffy™ (epinephrine nasal spray) FOR THE TREATMENT OF TYPE I ALLERGIC REACTIONS, INCLUDING ANAPHYLAXIS

ARS PHARMACUETICALS INC.

FDA ADVISORY BOARD BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse event
ARS	ARS Pharmaceuticals Inc.
ARS-1	0.3 mg epinephrine nasal spray suspension manufactured for ARS Pharmaceuticals Inc.
AUC	Area under the curve
$AUC_{(0-t)}$	Area under the plasma concentration-time curve to the final sample with a concentration ≥ LOQ
AUC_{last}	Area under the plasma concentration time curve from time zero to the time of the last quantifiable concentration
AUEC	Area under the effect curve.
AUEC $_{0-xmin}$	Area under the effect time curve from time zero to x minutes
$AUEC_{last}$	Area under the effect curve from time zero to the time of last reported PD measurement
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRF	Case report form
DBP	Diastolic blood pressure
DDM	Dodecylmaltoside
EAI	Epinephrine autoinjector
ER	Emergency room
E_{max}	Maximum observed effect
FDA	US Food and Drug Administration

ABBREVIATION	DEFINITION
GLP	Good Laboratory Practice
GRAS	Generally recognized as safe
HR	Heart rate
IFU	Instructions for Use
IgE	immunoglobulin E
IM	Intramuscular
IN	Intranasal
IV	Intravenous
kg	Kilogram(s)
L	left
mg	Milligram(s)
mL	Milliliter
MOA	Mechanism of action
NAC	Nasal allergy challenge
OR	Odds ratio
pAUC	Partial area under the curve
pAUEC	Partial area under the effect curve
PBAM	Physiologically based absorption model
PD	Pharmacodynamics
pg	Picogram
PK	Pharmacokinetics
POP PK	Population pharmacokinetics
PR	Pulse rate
R	Right

ABBREVIATION	DEFINITION
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
TEAE	Treatment-emergent adverse event
t_{Emax}	Time of maximum observed effect
t_{max}	Time to maximum plasma concentration
µL	Microliter
UDS	Unit Dose Sprayer
URTI	Upper respiratory tract infection
US/USA	United States of America
VAS	Visual Analog Scale

1. EXECUTIVE SUMMARY

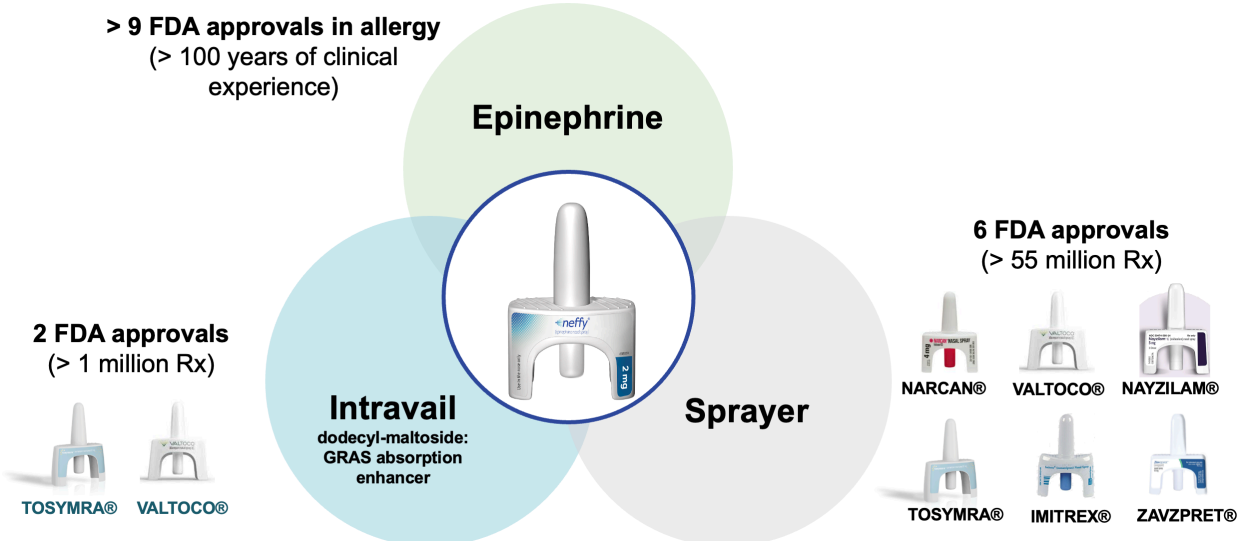
1.1. Introduction

This briefing document is being filed to the Pulmonary-Allergy Drugs Advisory Committee to support the review of ***neffy***™ (epinephrine nasal spray) 2 mg as a needle-free alternative to currently approved injection products for the treatment of Type I allergic reactions including anaphylaxis. The proposed Indication and Usage is as follows:

> ***neffy*** is indicated for the immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from insect stings or bites, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

neffy is an aqueous formulation of epinephrine (Figure 1) that includes a functional excipient dodecylmaltoside (DDM; tradename Intravail® A3). This excipient improves the bioavailability of the drug when administered with an aqueous solution (similar to saline) by the intranasal (IN) route and gives injection-like absorption without known injection-related adverse effects (e.g., pain or irritation). DDM, in the class of alkyl-glycosides, is considered Generally Recognized as Safe (GRAS) by the US FDA and is used in two FDA approved products in the United States (Tosymra® and Valtoco®). The Unit Dose Sprayer (UDS) device utilized to deliver ***neffy*** was originally introduced in 1997 and is approved for use with six branded products in the US including NARCAN® Nasal Spray, with more than 50 million prescriptions through 2022, and recently approved by FDA for over-the-counter use without training.

Figure 1: ***neffy Saline Based Epinephrine Nasal Spray: Triad of -Approved Components***



1.2. Pathophysiology of Type I Allergic Reactions and Anaphylaxis

Anaphylaxis is the most severe form of allergic reaction, or hypersensitivity reaction, and is almost always unexpected, and can be life-threatening (Tang-2009). The pathophysiology of anaphylaxis is primarily attributable to antigen-specific immunoglobulin E (IgE) activation and the subsequent activation of mast cells and basophils, ultimately leading to widespread release of histamine and other inflammatory mediators (e.g., cytokines). This histamine release results in generalized vasodilation, elevated heart rate, and increased vascular permeability (Peavy-2008), potentially leading to cardiovascular collapse.

Type I allergic reactions are potentially life-threatening hypersensitivity reactions that can occur within minutes of exposure to an allergen and generally require immediate treatment to relieve symptoms and prevent further progression. If not treated immediately, the reaction can progress to a more severe stage known as anaphylaxis that involves constriction of the airways, swelling of the throat, rapid heart rate, severe hypotension and other respiratory and cardiac symptoms that can develop and potentially present a life-threatening emergency.

The incidence of all-cause anaphylaxis in the United States has increased by 70% from 2004 to 2016. In 2016, the incidence rate was 218 per 100,000 persons in a patient population that was approximately 75% adults (Chaaban-2019).

Delay in treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters-2015). Overall rate of mortality from anaphylaxis in the United States is between 186 to 225 deaths per year (Ma-2013; Jerschow-2014). The vast majority of these deaths are persons that did not have epinephrine available at the time of the event or were not treated with epinephrine prior to emergency medical personnel could arrive (Poirot-2020).

1.2.1. Epinephrine's Mechanism of Action

Immediate administration of epinephrine is currently the first-line treatment for severe Type I allergic reactions (Shaker-2020) including anaphylaxis with more than 100 years of clinical experience. Epinephrine's Mechanism of Action (MOA) for the treatment of Type I allergic reactions and anaphylaxis is generally well understood and comes from direct systemic agonism of α- and β-adrenergic receptors, leading to a reversal of the pathological response to the histamine cascade caused by an antigen (Table 1).

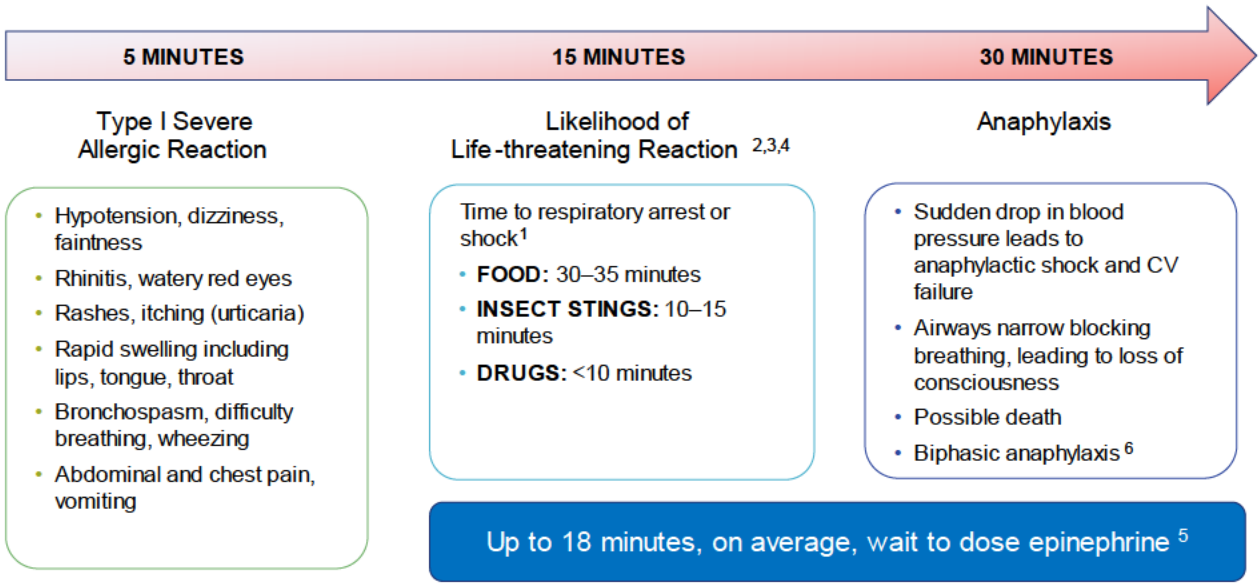
Table 1: Main Pharmacologic Effect of Epinephrine

Adrenergic Receptor	Pharmacological Effect of Agonism by Epinephrine	Clinical Effect of Agonism by Epinephrine
α1	• Increases **blood pressure** • Decreases mucosal edema	• Relieves hypotension and shock • Relieves upper airway obstruction
β1	• Increases blood pressure and **heart rate**	• Relieves hypotension and shock
β2	• Relaxation of bronchial smooth muscles • Increased skeletal muscle vasodilation • Inhibits inflammatory mediator release from mast cells and basophils	• Increase in bronchial airway • Increases blood flow to skeletal muscle • Reverses pathological histamine cascade

1.2.2. Early Intervention with Epinephrine is Critical

Symptoms of a Type I allergic reaction (Figure 2) are often variable and it can be difficult to predict severity and rate of progression of an episode. Because the clinical course of anaphylaxis can be unpredictable, prompt, and early use of epinephrine should be considered even with mild symptoms or single-system involvement (Shaker-2020). In the absence of clinical improvement, guidelines for the treatment of anaphylaxis recommend administering repeated doses of epinephrine every 5 to 15 minutes.

Figure 2: Early Intervention with Epinephrine – Time is Critical



1. Emergency treatment of anaphylactic reactions guidelines for healthcare providers. Resuscitation Council (UK) 2016 2. JF Philips et al. Allergy Asthma Proc (2011) 3. JT Fleming et al. J Allergy Clin Immunol Pract (2014) 4. E. Andrew et al. Prehospital Emergency Care (2018) 5. ARS market research 6. Liu 2020

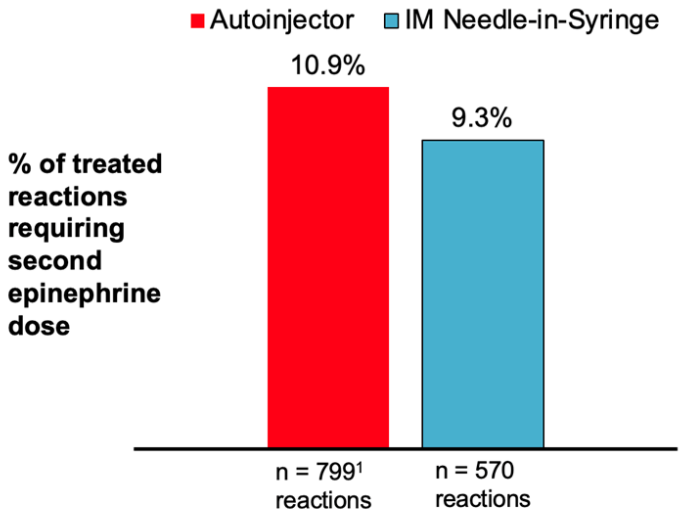
1.3. Current Treatment Options

The FDA has approved intramuscular and subcutaneous epinephrine injection and epinephrine autoinjectors including EpiPen®, Twinject®, Adrenaclick®, Auvi-Q®, Symjepi™, and as well as generic epinephrine autoinjectors. With exception of Auvi-Q, there were no clinical trials, nor PK studies, conducted to support approval of currently approved community use injection products and all were based on the observed efficacy of IM injection (needle & syringe) used in clinical settings. More recently it has been established that the different autoinjector products and manual IM injection with needle and syringe, all have very different pharmacokinetic profiles. Despite these pharmacokinetic differences the efficacy, all approved products in the treatment of severe allergic reactions including anaphylaxis are used interchangeably with the same guidance – immediately dose and wait 5 to 15 minutes to observe clinical response, then give a second dose if no response.

While controlled clinical trials have not been conducted with various epinephrine injection products, several studies have evaluated efficacy based on resolution of the allergic event after a single dose and the frequency with which a second dose was needed. Analysis of 21 studies that reported about second dose of epinephrine and identified the device used (Kahveci-2020, Oya-2020, Kondo-2018, Cardona-2017, Oren-2007, De Swert-2008, Johnson-2014, Nogic-2016, Grabenhenrich-2018, Campbell-2015b, Lee-2015, Ben Shoshan-2013, Soller-2019, White-2015, Arkwright-2009, Gold-2000, Webb-2006, Noimark-2012, Cardona-2020) suggests that autoinjectors (79.6% of these were EpiPen) and manual IM injection appear to be clinically comparable. The results of this analysis (Figure 3) demonstrated that second doses were required

in 10.9% of events (n=799) when an autoinjector was used and in 9.3% of events (n=570) when an IM needle and syringe was used.

Figure 3: Percent of Allergic Reactions Requiring a Second Dose, by Treatment—Results of a 12 Study Analysis



1.4. Unmet Medical Need

The importance of early epinephrine treatment immediately after symptoms or an allergic reaction are detected has been emphasized in the literature, guidelines and FDA approved product labeling (Fleming-2015, Sicherer-2017, Shaker 2020, Muraro-2021) for treatment of Type I allergic reactions and anaphylaxis.

It has been reported that delayed use of epinephrine has been associated with the following increased in serious outcomes (Patel-2021; EpiPen Package Insert-2020; Hochstadter-2016; Andrew-2018; Liu-2020; Fleming-2015; Turner-2017):

- Increased epinephrine requirement to control anaphylaxis symptoms (OR = 5.0)
- Abnormal vital signs – heat rate, systolic blood pressure, respiratory rate ($p<0.001$)
- Biphasic anaphylaxis (OR = 3.4)
- Risk factor for hospitalization (HR = 4.0)
- Fatality

However, even of those patients/caregivers who accept and fill a prescription, many either do not administer treatment entirely in an allergy emergency, or delay the use of epinephrine autoinjectors (EAIs) until symptoms progress to a more severe state, even when the patient or caregivers knows they are having a severe allergic reaction (Asthma and Allergy Foundation of

America-2019; Noimark-2012; Brooks-2017; Fleming-2015). These limitations are primarily driven by fear of the needle (needle phobia), concerns about safety, complexity of the device and concerns about having to go to the emergency room (ER) after dosing, often resulting in hesitancy to use the devices, delayed treatment, and an increased risk of serious complications and hospitalizations (Sampson-1992; Søreide-1988; Pumphrey-2000, Casale 2022).

The most common concerns contributing to not having epinephrine present at all or dosing delays leading to worse outcomes in an allergy emergency are listed in the Table 2, with a detailed discussion provided in Section 2.4.

Table 2: Unmet Needs and Product Attributes to Address

Reasons for delaying or not administering epinephrine		**Product attributes needed**
Never filling prescription	~43% of attempted Rx by doctors are rejected by patients and caregivers (Cohen 2021)	Smaller, needle-free, pain-free, easier to use devices
Lack of carriage	Too large to fit in pocket (~50% do not carry one, <10% carry two devices) (Warren-2018)	Smaller more portable devices
Fear of the needle	Needle phobia is the primary cause for failure to administer (25%-50% of events) or delayed treatment (until more severe and up to 18 minutes in studies) with epinephrine when needed (Noimark-2012; Fleming-2015; Brooks-2017)	Needle-free, pain-free
Concerns about safety	Lacerations, injection into bone, IV bolus injection, & accidental self-injection (Brown-2016; Kim 2017; Ebisawa-2022; Anshien-2019)	Needle-free, Patient education
Complex administration	23 to 35% error rate after training; Multiple device reliability recalls/warnings by FDA (El Turki-2017; FDA-2015; 2017; 2020; 2022)	Easy to use device, Rapid to administer, intuitive to use devices, Reliable
Uncertainty if symptoms warrant use	Wait until disease progresses to a severe state	Patient education regarding safety of epinephrine, Needle-free, pain-free device
Availability	Epinephrine not available in public locations due to injection related risks	Needle-free; intuitive to use devices

As a result of these limitations, a significant proportion of the approximate 40 million patients at risk of severe Type I allergic reactions in the United States do not receive or fill prescriptions for intramuscular injection products, such as EpiPen or generic equivalents. Of the 3.3 million patients who fill their prescriptions in the US, fewer than half carry the intramuscular injectable products with them on a regular basis, while many of the other half delay treatment during a severe type I allergic reaction (Brooks-2017; Fleming-2015). This hesitancy results in the prolonging troublesome symptoms and an increased risk of progression of the reaction to anaphylaxis, including possible long-term comorbidities or even death (Warren-2018).

Therefore, there is a significant unmet need to address these issues as many patients and caregivers are unwilling to use a needle-bearing device. ***neffy*** has the potential to address many of these unmet medical needs as needle-free option to current injection devices (Table 17).

1.5. Clinical Program

neffy's clinical development program is centered on:

1. Bracket approach: the rationale that a single dose of ***neffy*** has a pharmacokinetic profile that is similar to other injection products and bracketed by EpiPen 0.3 mg and Epinephrine 0.3 mg IM (discussed in Sections 1.5.1, 4.1 and 4.2) with other approved injection devices also within this bracket; and

2. The use of pharmacodynamic data as a surrogate for efficacy (discussed in Sections 1.5.2 and 4.3);

3. With repeat dose of ***neffy*** a pharmacokinetic profile greater than injection products is warranted given the more serious nature of the disease including hypotension. ***neffy*** is dose proportional with repeat dosing and between doses, while injection products have been proven to not be dose proportional.

1.5.1. Bracket Approach for Pharmacokinetics

Approved epinephrine injection products have been shown to be highly variable from study to study (Figure 4) (Lockey-2022, Turner-2022) with a median T_{max} values ranging from 5 to 60 minutes and mean maximum concentration (C_{max}) values ranging from 209 to 869 pg/mL (Table 3). The pharmacokinetic variability observed across the injection products is likely driven by multiple factors including the type of device used, needle length, force of injection, location of injection, and injection technique (Section 4.1).

In fact, EpiPen itself is highly variable and results from multiple studies since 2012 using modern bioanalytical techniques demonstrate a wide range of results across studies. ***neffy*** 2 mg is bracketed by these results and more consistent across studies then EpiPen (Appendix 1).

ARS initiated the development program with ***neffy*** 1 mg, which was similar to IM injection (needle and syringe) and bioequivalent in at least one early study. ARS later decided to increase the ***neffy*** dose to 2 mg and discussed this with FDA given the wide range of pharmacokinetics observed with out of hospital use autoinjectors being revealed in ARS and other published studies (Appendix 1). FDA and ARS agreed at the time that the lower limit for epinephrine exposure with ***neffy*** 2 mg should result in a higher C_{max} and faster T_{max} as compared to the reference listed product IM adrenalin injection to ensure efficacious systemic exposures of epinephrine. At the same time, to ensure safety, FDA suggested that the upper limit of exposure based on C_{max} from ***neffy*** 2 mg after a first dose should not exceed that of EpiPen.

Thus, in agreement with FDA and as described above, a bracketing approach was used to demonstrate ***neffy*** would result in pharmacokinetics within the range of that known to be efficacious and safe on a first dose. I M injection (needle and syringe) was selected as the reference listed drug (RLD) for efficacy with ***neffy*** pharmacokinetics being greater and more rapid than IM. EpiPen, while highly variable from study to study (Appendix 1), exhibits the highest exposures and most rapid T_{max} and was used as the upper reference in the bracket to ensure epinephrine exposures were in a safe range (Table 4). While overall AUC_{0-t} is not considered an important factor for efficacy, FDA requested that ARS include dosing with the approved safe 0.5 mg IM injection dose as an upper bracket to confirm safety.

Figure 4: Variable Pharmacokinetic Profiles of Epinephrine Injection from ARS Studies

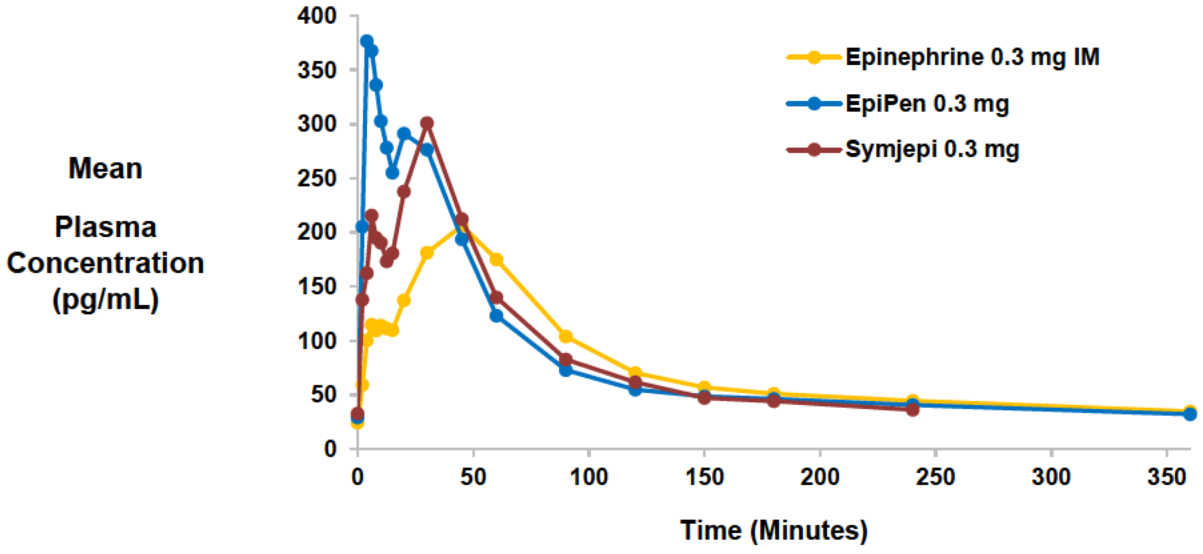


Table 3: PK Parameters Across Representative FDA Approved Injection Products

Treatment*	Source	N	Mean Study C_{max} (pg/mL)	Median or Mean Study T_{max} (min)	Study T_{max} Range (min) in individuals
Epinephrine 0.3 mg IM	Literature	200	209 – 489	30 – 60	3 – 120
	ARS*	223	244 – 339	45	3.9 – 360
Symjepi 0.3 mg	ARS*	36	438	30	4 – 90
Auvi-Q 0.3 mg**	Literature	67	486	20	5 – 60
EpiPen 0.3 mg	Literature	311	288 – 869	5 – 40	1 -120
	ARS*	113	375 – 753	7.5 – 24	2 – 154
Total Range			**209 – 869**	**5 – 60**	**1 – 360**

*ARS data = EPI 03, 04, 07, 12, 15, 16, and 17 Studies; **Baseline corrected

Table 4: Bracket Approach for Pharmacokinetics (Based on First Dose Only)

Bracketing Criteria	Lower Bracket	Upper Bracket
C_{max} (primary)	0.3 mg IM	0.3 mg EpiPen
T_{max} (primary)	0.3 mg IM	0.3 mg EpiPen
$pAUC_{0\text{-}20,\ 0\text{-}30,\ 0\text{-}45}$ (primary)	0.3 mg IM	0.3 mg EpiPen
$AUC_{0\text{-}t}$ (secondary)		0.5 mg IM

1.5.2. Pharmacodynamic Data as a Surrogate for Efficacy

Randomized, controlled clinical studies of the treatment of patients at risk of anaphylaxis are generally considered unethical and/or impractical and no such comparative efficacy study with epinephrine has ever been conducted in patients at risk of serious allergic reactions and anaphylaxis.

On the other hand, epinephrine's MOA for the treatment of Type I allergic reactions and anaphylaxis is well understood and comes from direct systemic agonism of α- and β-adrenergic receptors, leading to a reversal of the pathological response to the histamine cascade caused by an antigen (Table 1).

Therefore, in collaboration with the FDA, pharmacodynamic (PD) endpoints were used as surrogate markers for efficacy, with the understanding that these endpoints (blood pressure and heart rate) are indicative of α- and β-adrenergic receptor activation and, consequently, clinical efficacy. Throughout the clinical development program, ***neffy***'s efficacy and safety has been established based on a series of clinical studies in both healthy volunteers and patients with allergy. While studies were done in Type I allergy patients or healthy volunteers who were not having anaphylaxis, there is no scientific reason that receptor binding would change during anaphylaxis and thus these studies are considered predictive of efficacy.

1.5.3. Evaluation of Various Dosing Conditions

Because both ethical and practical limitations preclude the conduct of clinical trials in patients experiencing severe allergic reactions and anaphylaxis. Therefore, ARS conducted a GLP study using a dog anaphylaxis model to assess absorption during acute anaphylaxis. Further, ARS conducted two clinical trials to assess the pharmacokinetics and pharmacodynamics of ***neffy*** 2 mg in subjects with allergic rhinitis (EPI 16) and upper respiratory tract infections (EPI 14) in order to evaluate the effect of nasal edema and congestion on the absorption of epinephrine administered via ***neffy*** 2 mg. Two additional studies, EPI 04 (NAC rhinitis) and EPI JP01 (Pollen induced rhinitis), were also conducted with ***neffy*** 1 mg dose as supportive but are not reported in detail in this summary.

1.6. Integrated Pharmacokinetic and Pharmacodynamic Analysis

The primary ***neffy*** 2 mg and supportive ***neffy*** 1 mg studies conducted to support approval are summarized in Table 5. ARS started the development program with ***neffy*** 1 mg, which exhibited similar pharmacokinetics to 0.3 mg IM injection. Subsequently, given the PK range of FDA approved community-use injection products, ARS decided to increase the dose to 2 mg considering its out of hospital use. A summary of key PK and PD findings from an integrated PK and PD analysis is presented below (Section 1.6.1), with an in-depth discussion of the comparative PK and PD results presented in Section 5.

Table 5: Summary of Primary (*neffy* 2 mg) and Supportive (*neffy* 1 mg) Clinical Pharmacology Studies (abbreviated)

Neffy Dose	Study No.	Patient Population
***neffy* 2 mg (primary)**	**EPI 15**	Adult: Healthy volunteer
	EPI 16	Adult: Type I allergy patients (NAC induced rhinitis)
	EPI 17	Adult: Type I allergy patients with self-administration
	EPI 10	Pediatric: Type I allergy patients ≥ 30 kg
***neffy* 1 mg (supportive)**	**EPI 03**	Adult: Healthy volunteer
	EPI 04	Adult: Type I allergy patients (NAC induced rhinitis)
	EPI 07	Adult: Healthy volunteer
	EPI 12	Adult: Type I allergy patients with self-administration
	EPI JP01	Adult: Type I allergy patients (Pollen induced rhinitis)

Additionally, Population Pharmacokinetic assessments (POP PK) and Physiologically Based Absorption Model (PBAM) were conducted. The PBAM modeling is a more advanced method of modeling both PK and PD effects of drugs that considers data from clinical studies as well as hundreds of physiological and metabolic factors in humans. This PBAM model was developed specifically for ***neffy*** as the first known specific model to replicate nasal absorption at the University of Florida.

Ongoing studies include the EPI 10 clinical trial in Type I allergy patients 15 kg to <30 kg body weight as well as two Phase 2 studies in patients with urticaria and asthma patients.

This integrated analysis presents the pharmacokinetics and pharmacodynamics of 1 mg and 2 mg doses of ***neffy*** relative to both manual IM injection and EpiPen using data from five randomized, open-label, single-dose phase 1 trials (EPI 03, EPI 04, EPI 07, EPI 15, and EPI 16).

1.6.1. Integrated Pharmacokinetics Results

When administered once, the pharmacokinetic profile of ***neffy*** 2 mg was bracketed by approved injection products. ***neffy*** demonstrated greater and more rapid exposure compared to Epinephrine 0.3 mg IM (the basis for efficacy) and a lower C_{max} and more controlled absorption relative to EpiPen (the upper limit for safety) (Figure 5).

When administered twice, ***neffy*** resulted in a dose proportional increase in epinephrine concentrations (Figure 6). ***neffy's*** dose proportionality may be particularly advantageous during more severe Type 1 allergic reactions, when a second dose is necessary to achieve an acceptable therapeutic effect. Data in multiple studies on twice dosing with both manual IM injection of epinephrine (needle and syringe) and EpiPen does not result in dose proportional increase in exposures and is only about 30-60% more than a single dose across all studies. This phenomenon may be caused by epinephrine's effect in increasing the blood flow into the skeletal muscle in the thigh that is more prominent following the first injection by IM injection (Tanimoto-2022).

Figure 5: Plasma Concentration vs Time Profiles of Epinephrine Single and Twice Dosing

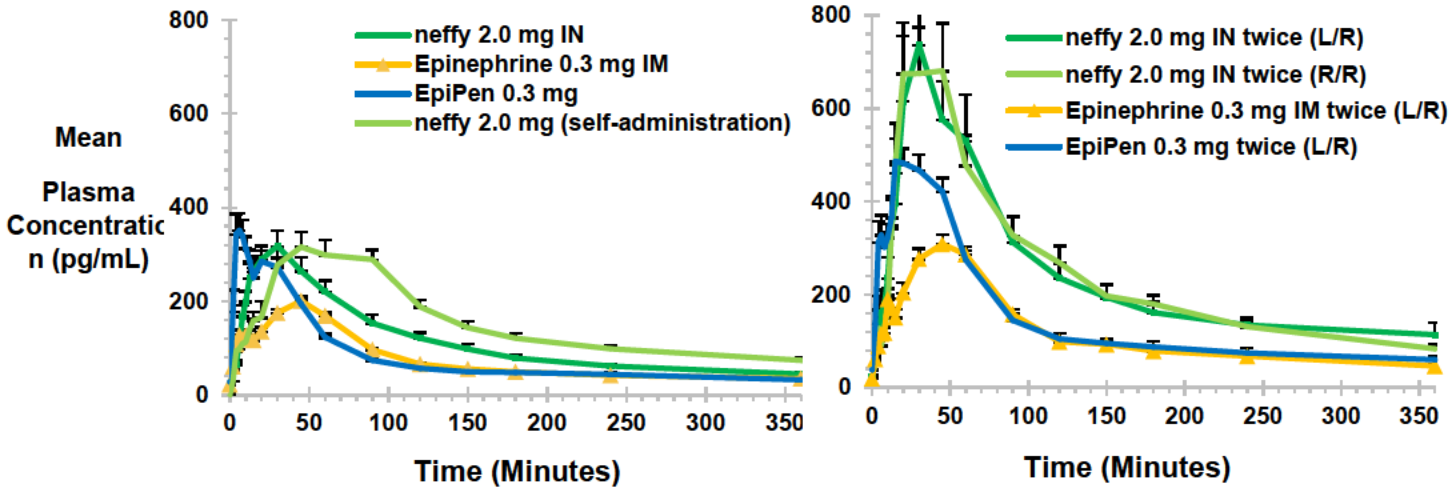


Table 6: Pharmacokinetic Parameters of Single dosing, by Treatment (Bracketing)

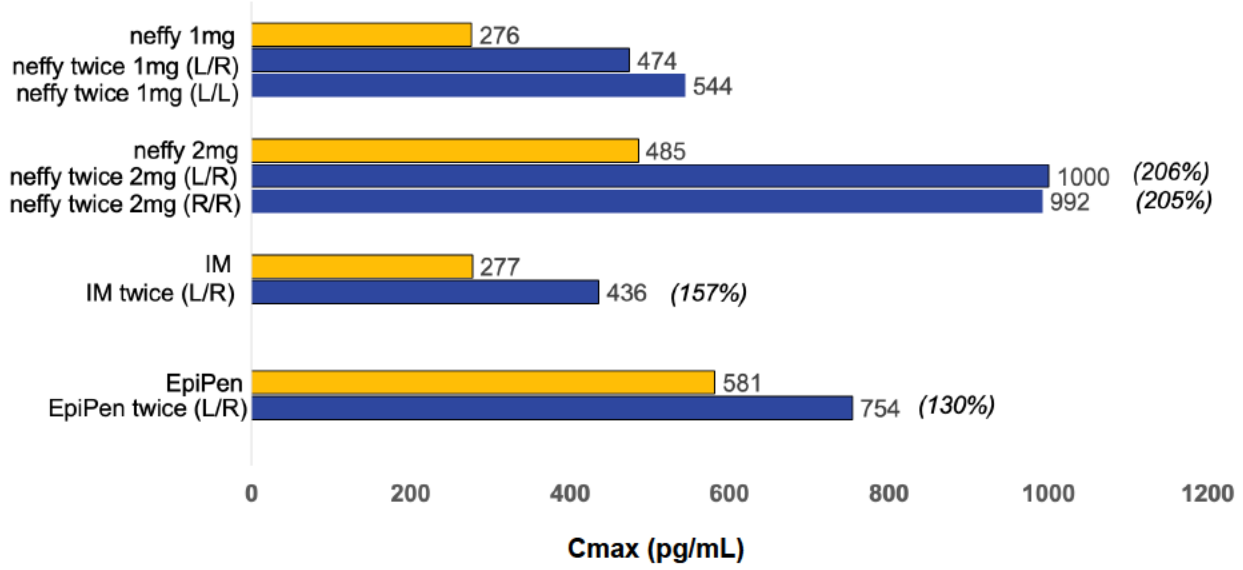
Product	N	C_{max}	T_{max}	$pAUC_{0-20}$	$pAUC_{0-45}$	AUC_{0-t}
		(pg/mL) Mean (CV%)	(minutes) Median (range)	(min*pg/mL) Mean (CV%)		
Epi 0.3 mg IM	178	277 (65)	45 (4-360)	2090 (86)	6290 (61)	27900 (39)
neffy* 2 mg (self-administration)	**42**	**421 (66)**	**30 (6-240)**	**2964 (71)**	**10545 (63)**	**46776 (56)**
***neffy* 2 mg**	**78**	**485 (71)**	**20.5 (2-150)**	**3610 (84)**	**11000 (76)**	**40900 (68)**
EpiPen 0.3 mg	77	581 (76)	10 (2-45)	5640 (73)	12000 (53)	31600 (39)

* EPI 17 Study; Note: mean AUC0-t of Epinephrine 0.5 mg was 43700 min*pg/mL

Table 7: Pharmacokinetic Parameters of Twice Dosing, by Treatment

Treatment	N	C_{max} (pg/mL)	$pAUC_{0-20}$ (min*pg/mL)	$pAUC_{0-45}$ (min*pg/mL)	AUC_{0-t} (min*pg/mL)	t_{max} (min)
		Mean (%CV)				median (range)
***neffy* 2 mg twice (L/R)**	**39**	**1000 (93)**	**5430 (99)**	**22000 (97)**	**86000 (77)**	**30 (6 -150)**
***neffy* 2 mg twice (R/R)**	**39**	**992 (75)**	**5610 (94)**	**22500 (82)**	**86500 (61)**	**30 (4 – 150)**
Epinephrine 0.3 mg IM twice (L/R)	70	436 (49)	2750 (83)	9610 (59)	47500 (33)	45 (6 – 180)
EpiPen 0.3 mg twice (L/R)	78	754 (65)	6930 (77)	18300 (54)	55000 (48)	20 (4 – 360)

Figure 6: PK Dose Proportionality Based on Mean C_{max}



1.6.2. Integrated Pharmacodynamics Results

In general, ***neffy*** 2 mg dosed once resulted in pharmacodynamics responses that were comparable to or better than injection products (Figure 7). Changes and absolute values of blood pressure and heart rate were within normal physiologic levels as observed during daily activities such as exercise or climbing several flights of stairs. Change from baseline for systolic blood pressure and heart rate were similar (not significantly different) from EpiPen, but generally statistically greater than 0.3 mg IM injection. For diastolic blood pressure there was a greater drop after EpiPen or IM injection than with intranasal administration due to the direct to systemic route of administration (i.e., similar to intravenous infusion) (Tanimoto-2022).

With twice dosing of ***neffy*** 2 mg (Figure 8) pharmacodynamic responses were generally statistically greater for systolic blood pressure increase as compared to EpiPen and IM injection. This greater mean increase in systolic blood pressure is likely due to the fact that the pharmacokinetics of injection products are not dose proportional and the significant drop in diastolic blood pressure that suppresses the increase in systolic blood pressure. However, given that when a second dose is needed the reaction is generally more severe and the patient is more likely hypotensive due to vasodilation from histamine and other mediators, ***neffy***'s greater increase in systolic blood pressure is generally considered beneficial. Changes in heart rate were similar to EpiPen (not significantly different) but greater than IM injection.

Figure 7: Single Dose: Mean Change from Baseline PD vs Time and Box Plots

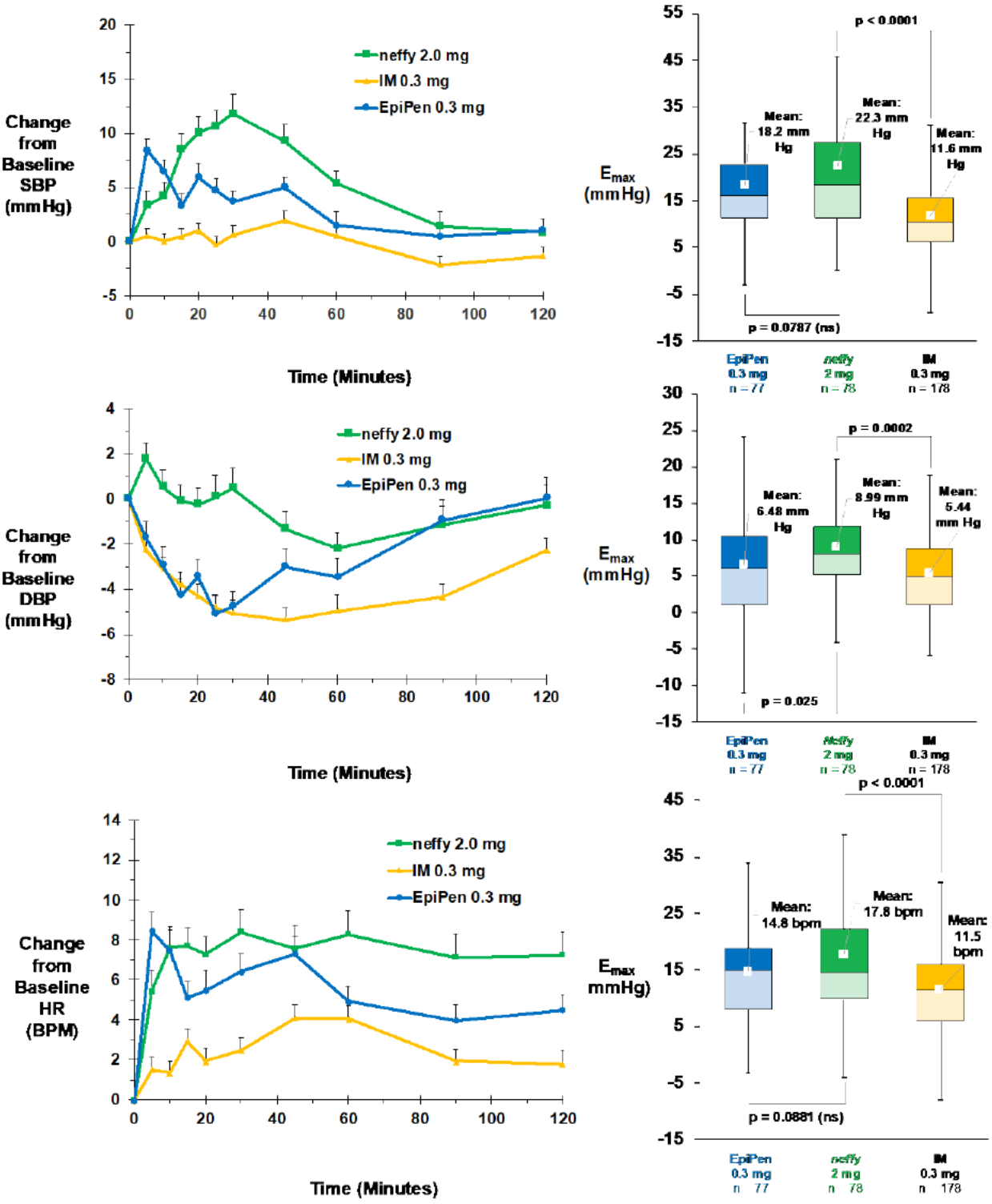
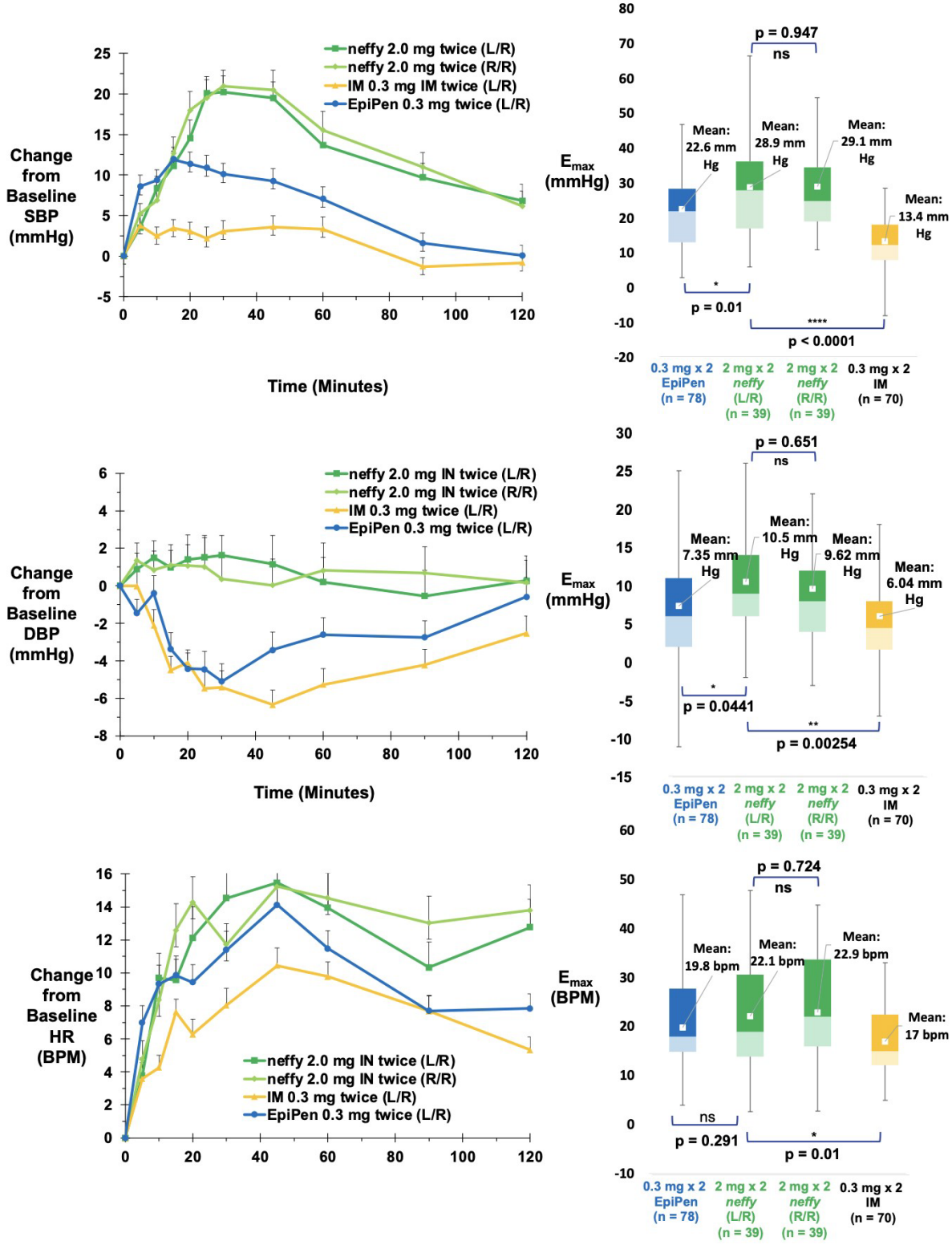


Figure 8: Twice Dosing: Mean Change from Baseline PD vs Time and Box Plots



1.6.2.1. Differences in Pharmacodynamic Response by Route

The pharmacodynamic results were mostly comparable between ***neffy*** and EpiPen despite the higher and faster pharmacokinetic profile of EpiPen. The greater drop in the DBP following IM injection products may be attributed to direct epinephrine injection into the skeletal muscle in the thigh. β_2 adrenergic receptors promote vasodilation in the skeletal muscle, causing a decrease in peripheral vascular resistance and increased blood flow to skeletal muscle, ultimately resulting in a decrease in DBP (Westfall-2011), which may occur by direct injection into the thigh (100% epinephrine in the thigh) than the routes avoiding injection into the thigh. (Tanimoto-2022) (Section 5.2.3 for detail explanation). This drop in DBP after initial IM injection of epinephrine suppresses the increase in SBP and in theory may be negative in persons with significant hypotension.

1.6.3. Pediatric Pharmacokinetics and Pharmacodynamic Results

The pharmacokinetic results of the interim analysis (Table 8) demonstrate that in children ≥30 kg, ***neffy*** 2 mg results in epinephrine absorption that is comparable-to-slightly higher than what is observed in adults. This was further supported by simulations based on the PBAM and POP PK models. Epinephrine levels between the 1 (previous dose) and 2 mg doses in children ≥30 mg appear to be dose proportional.

Table 8: Summary Statistics of Epinephrine Pediatric Pharmacokinetic Parameters by Treatment

Product	N	Mean C_{max} (pg/mL) (CV%)	Median t_{max} (minutes) (range)	$pAUC_{0-20}$ (min*pg/mL) Mean (CV%)	$pAUC_{0-45}$ (min*pg/mL) Mean (CV%)	AUC_{0-t} (min*pg/mL) Mean
neffy 1.0 mg Children ≥ 30 kg (previous dose)	25	253 (66)	20 (8-120)	2570 (78)	5960 (52)	14000 (53)
neffy 2.0 mg Children ≥ 30 kg	16	540 (71)	25 (3-120)	4140 (78)	13500 (76)	35500 (76)
neffy 2.0 mg Adults (Integrated)	78	485 (71)	21 (2-150)	3610 (84)	11000 (76)	40900 (68)

1.6.4. Evaluation of Various Dosing Conditions

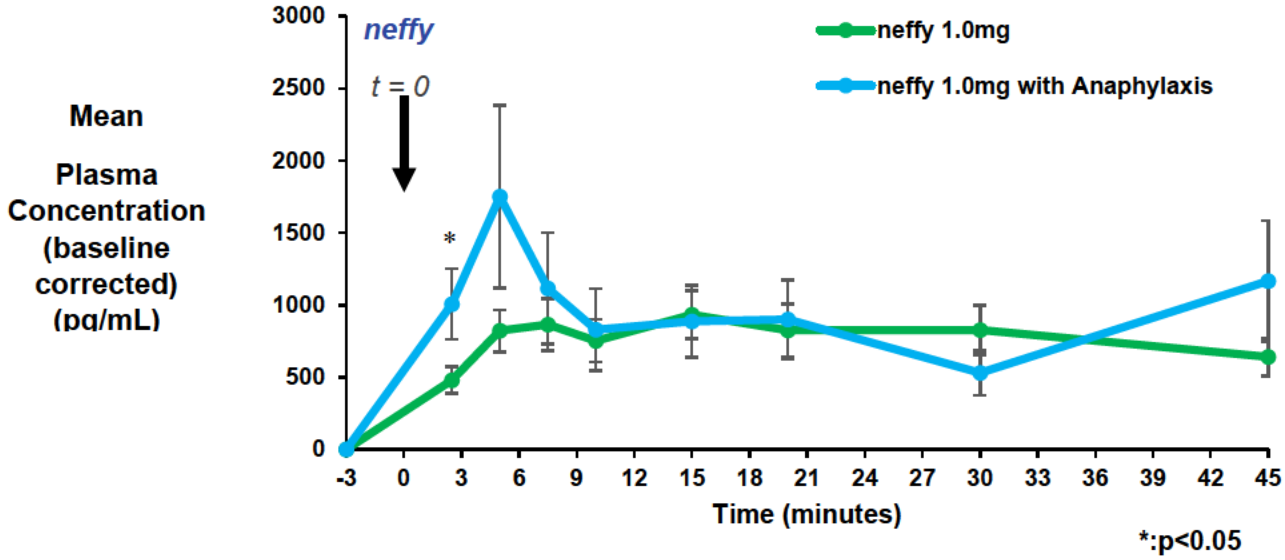
Since both ethical and practical limitations preclude the conduct of clinical trials in patients experiencing severe allergic reactions and anaphylaxis ARS conducted a GLP study using a dog anaphylaxis model to assess absorption during acute anaphylaxis. Furthermore, ARS conducted two clinical trials to assess the pharmacokinetics and pharmacodynamics of ***neffy*** 2 mg in subjects with allergic rhinitis (EPI 16) and upper respiratory tract infections (EPI 14) in order to evaluate the effect of nasal edema and congestion on the absorption of epinephrine administered via ***neffy*** 2 mg.

1.6.4.1. Effect of Hypotension during Anaphylaxis (GLP Dog Anaphylaxis Model)

A GLP study using a dog anaphylaxis model was conducted to evaluate the pharmacokinetics of ***neffy*** in anesthetized beagle dogs under both normal conditions and Tween 80-induced anaphylaxis conditions. A total of 14 dogs (10 males and 4 females) were dosed with ***neffy*** 1 mg under normal conditions, followed by ***neffy*** 1 mg under anaphylaxis conditions. All dogs showed signs of allergic reaction/anaphylaxis following administration of Tween 80.

Absorption during an anaphylactic reaction with severe hypotension (61±10/39±7 mmHg) was confirmed to be at least as good as when the dogs were in a normal state.

Figure 9: Absorption During Hypotension: GLP Dog Anaphylaxis Model (Baseline Corrected)



1.6.4.2. Effect of Allergic Rhinitis (EPI 16)

EPI 16 was conducted to evaluate the comparative bioavailability of ***neffy*** 2 mg with and without induced allergic rhinitis by nasal allergen challenge (NAC) relative to Epinephrine 0.3 mg IM. EPI 16 was conducted under worst case dosing conditions with ***neffy*** administered immediately after NAC induction when symptoms of congestion and rhinorrhea were greatest.

EPI 16 utilized the Total Nasal Symptom Score (TNSS) questionnaire to evaluate the nasal symptoms per FDA's guideline (Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry). ***neffy*** 2 mg was administered immediately after rhinitis was induced when symptoms such as congestion and rhinorrhea were most significant.

The criteria for subjects to be dosed with ***neffy*** 2 mg in the EPI 16 clinical study was that they had to have a TNSS of ≥5 out of 12 and a congestion score of ≥2 out of 3 for at least one allergen

during the screening challenge. There were 30 of the 34 subjects who reported positive symptoms of rhinorrhea (runny nose) based on the TNSS scoring after NAC induction and before dosing of ***neffy*** 2 mg.

Pharmacokinetic Results

Relative to normal nasal conditions, allergic rhinitis resulted in a more rapid (T_{max}) absorption of epinephrine (Figure 10 and Table 9), presumably due to increased permeability which was observed in the anaphylaxis dog model (Section 1.6.4.1) and also is reported in the literature (Tuttle-2020). The T_{max} with ***neffy*** 2 mg with rhinitis was 7 minutes as compared 20 minutes in the normal nasal state. T_{max} with ***neffy*** 2 mg with rhinitis was also significantly more rapid than IM epinephrine injection (7 min vs. 45 min, $p<0.0001$).

At the same time, ***neffy*** 2 mg with rhinitis resulted in more rapid clearance (i.e., lower C_{max} and overall AUC_{0-t}) compared to normal nasal conditions, which may be due to rhinitis symptoms such as associated rhinorrhea (i.e., more rapid nasal fluid flow resulting in increased clearance of drug from the nasal mucosa). Rhinorrhea was observed in most of the subjects (30 of 34 subjects in the rhinitis group). While the C_{max} was lower with rhinitis as compared to that with ***neffy*** 2 mg in the normal nasal state, the maximum exposure (C_{max}) with rhinitis was still comparable to IM Epinephrine 0.3 mg (Cmax 303 vs 259 pg/mL, $p>0.05$).

Figure 10: Plasma Concentration vs Time Profiles of Epinephrine in neffy Subjects with Rhinitis and Normal Nasal Conditions (EPI 16)

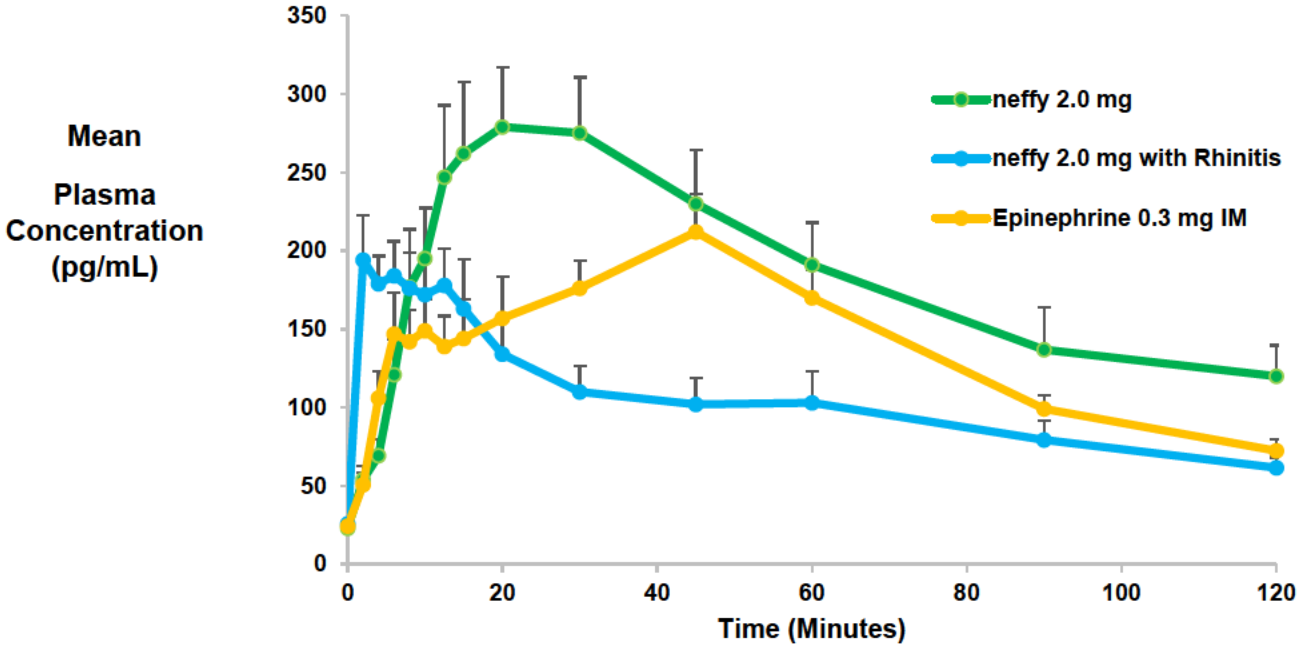


Table 9: Pharmacokinetic Parameters, by Treatment (EPI 16)

Treatment	N	T_{max} (min) median (range)	C_{max} (pg/mL) mean (%CV)	AUC_{last} (min*pg/mL) mean (%CV)
***neffy* 2.0 mg**	36	20 (2 – 120)	491 (65.2)	37100 (66.1)
***neffy* 2.0 mg with rhinitis**	34	7 (2 – 90)*	303 (67.7)	23300 (69.0)
Epinephrine 0.3 mg IM	35	45 (4 – 360)	259 (61.7)	26000 (41.9)

*neffy 2.0 mg with rhinitis vs. Epinephrine 0.3 mg IM: tmax ($p<0.0001$) : C_{max} and AUC_{last} were not statistically different

As see in Table 10 below, ***neffy*** 2 mg with rhinitis results in epinephrine exposures that are significantly greater then IM injection from 2 minutes after administration (first time point) and through the first 30 minutes followed by comparable exposures.

Table 10: Partial AUC Results (EPI 16)

Treatment	N	pAUC (min*pg/mL)						
		AUC_{0-2min}	AUC_{0-4min}	AUC_{0-6min}	AUC_{0-8min}	$AUC_{0-10min}$	$AUC_{0-12.5min}$	$AUC_{0-15min}$
		mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)
ARS-1 2.0 mg	36	77.1 (83.4)	201 (81.0)	391 (81.9)	688 (90.5)	1060 (92.8)	1630 (85.6)	2270 (83.5)
ARS-1 2.0 mg with rhinitis	34	212* (78.9)	569* (69.1)	922* (60.1)	1270* (58.0)	1610* (57.8)	2050* (56.4)	2460* (58.7)
Epinephrine IM 0.3 mg	35	68.5 (69.6)	211 (69.7)	439 (78.7)	700 (82.7)	966 (79.8)	1290 (77.4)	1610 (77.7)
Treatment	**N**	**pAUC (min*pg/mL)**						
		$AUC_{0-20min}$	$AUC_{0-30min}$	$AUC_{0-45min}$	$AUC_{0-60min}$	$AUC_{0-120min}$	AUC_{0-6h}	AUC_{1-6h}
		mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)
ARS-1 2.0 mg	36	3630 (78.7)	6400 (67.1)	10200 (62.4)	13400 (62.1)	22200 (65.7)	38700 (62.2)	25000 (76.8)
ARS-1 2.0 mg with rhinitis	34	3200* (65.9)	4400* (70.9)	5970 (72.9)	7500 (76.4)	12400 (77.7)	24000 (66.0)	16500 (64.8)
Epinephrine IM 0.3 mg	35	2280 (79.5)	3790 (76.5)	6430 (69.8)	9030 (66.3)	15200 (54.5)	27000 (39.1)	17800 (38.0)

* neffy 2.0 mg with rhinitis vs. Epinephrine 0.3 mg IM: pAUC 2 to 20 min ($p<0.01$), 30 min ($p<0.05$)

If evaluating PK results based on absolute concentrations (Table 11), the concentration of epinephrine after administration of ***neffy*** 2 mg with rhinitis is greater than IM injection after the first time point at 2 minutes and through 20 minutes after dosing where the concentration are similar and not significantly different. ***neffy*** 2 mg with rhinitis was statistically greater than IM injection at the 2 and 4 minute time points after dosing.

Table 11: Summary Statistics of Epinephrine C_{max} By Time Point Results (EPI 16)

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL) Mean (%CV)	Epinephrine Concentration at Each Time Point mean (%CV)					
				2 min	4 min	6 min	10 min	15 min	20 min
ARS-1 2.0 mg	36	20.0 (2-120)	491 (65.2)	54 (95)	70 (88)	121 (113)	195 (97)	262 (103)	279 (82)
ARS-1 2.0 mg with rhinitis	34	7.00 (2-90)	303 (67.7)	194* (85)	179* (56)	184 (68)	172 (74)	163 (109)	133 (100)
Epinephrine IM 0.3 mg	35	45.0 (4-360)	259 (61.7)	51 (84)	106 (86)	147 (99)	149 (75)	144 (95)	157 (93)

* neffy 2.0 mg with rhinitis vs. Epinephrine 0.3 mg IM: 2 to 4 min ($p<0.01$); 6 to 20 min were no significantly different

Clinical effect with epinephrine is observed within 5 to 10 minutes after administration of IM injection with approximately 90% of all events resolving with a single dose and only approximately 10% requiring a second administration to resolve symptoms (Patel-2021). The need for a second dose is also related to severity of the event and if epinephrine administration was delayed (Hochstadter-2016, Patel-2021), and thus with prompt administration after symptoms are detected the need for a second dose may be further reduced. Prescribing guidelines (Shaker-2020) are clear that administration of a second dose of epinephrine should occur if response is not observed in 5 to 10 minutes.

Thus, ***neffy*** 2 mg even with NAC induced rhinitis will give greater or similar exposure of epinephrine on a first dose than IM injection through the first 45 minutes based on partial exposures (AUC) and through the first 20 minutes based on absolute concentration. If a second dose of epinephrine is administered with either ***neffy*** 2 mg or IM injection, the additional administration would occur before IM injection reaches peak concentration (t_{max} = 45 minutes) and in the time frame where ***neffy*** 2 mg has overall higher exposures compared to IM through at least 20 minutes. Therefore, even more rapid clearance of the drug from the nasal mucosa that may occur from rhinorrhea during allergic rhinitis, is not anticipated to result in any clinically meaningful difference in effectiveness relative to IM injection of epinephrine. If effect is not observed in the first 5 to 10 minutes, a second dose would be given per dosing guidelines. The second dose would likely have absorption more similar to dosing with normal nasal conditions given the known effect of epinephrine to rapidly reverse nasal congestion and rhinorrhea (Macmillan-2022).

Pharmacodynamic Results

The overall pharmacodynamic effect of ***neffy*** 2 mg with rhinitis was similar to both doses of IM Epinephrine (Figure 11 and Table 12).

Figure 11: EPI 15 PD Results: Box Plots

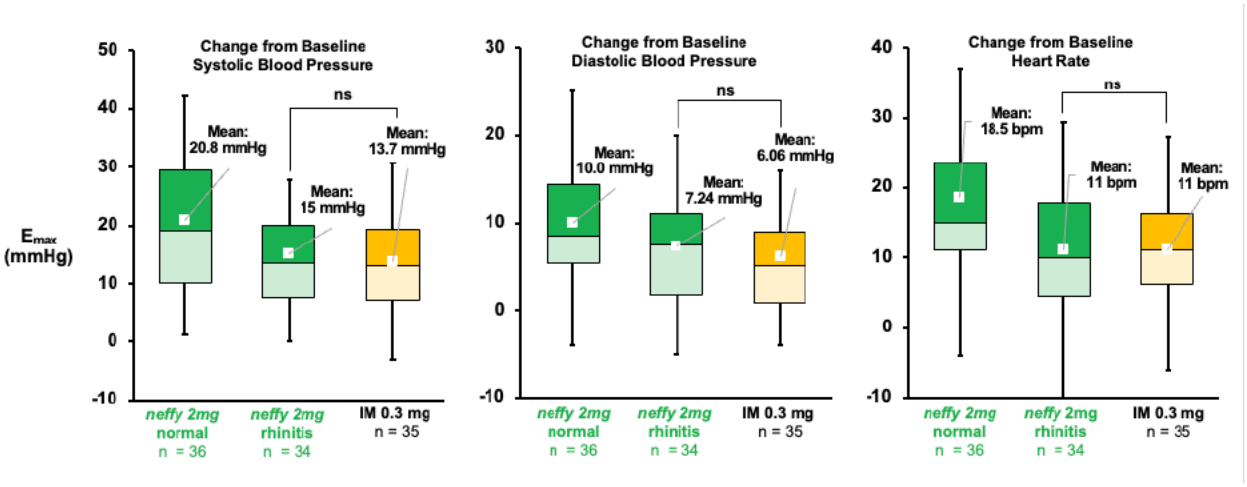


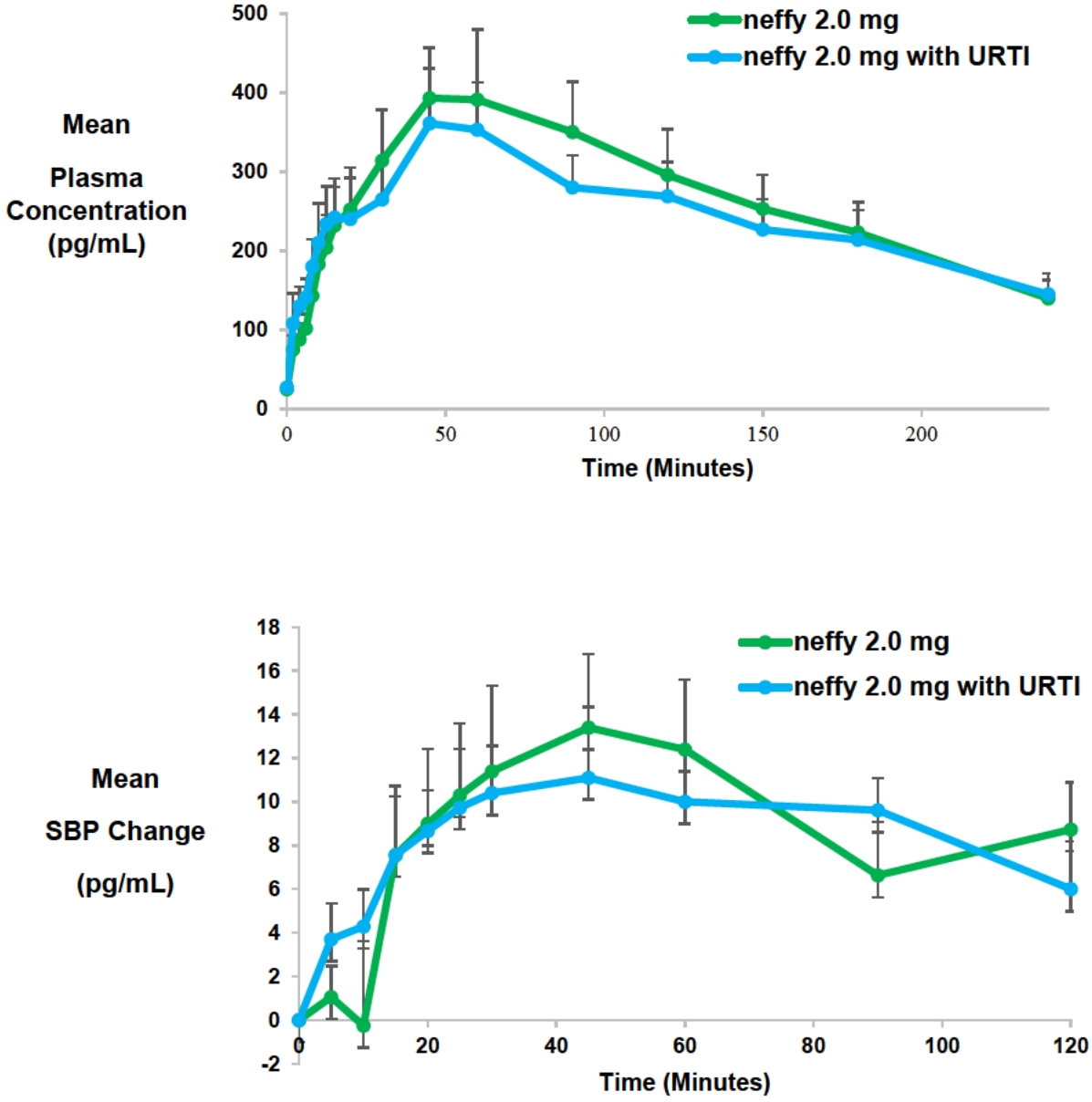
Table 12: Pharmacodynamic Parameters, by Nasal Condition

Treatment	N	E_{max} mean (%CV)			T_{Emax} median (range)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
***neffy* 2 mg**	36	20.8 (80.6)	10.0 (77.2)	18.5 (75.9)	26.0 (1.00-120)	25.0 (1.00-120)	25.0 (1.00-178)
***neffy* 2 mg with rhinitis**	34	15.0 (83.4)	7.24 (6.56)	11.0 (111)	19.0 (1.00-120)	27.5 (1.00-119)	9.00 (1.00-119)
Epinephrine IM 0.3 mg	35	13.7 (71.1)	6.06 (128)	11.0 (70.6)	19.0 (1.00-123)	15.0 (1.00-123)	44.0 (2.00-120)

1.6.4.2.1. Effect of Upper Respiratory Tract Infection (EPI 14)

EPI 14 was conducted to evaluate the comparative bioavailability of ***neffy*** 2 mg with and without nasal edema and congestion resulting from an upper respiratory tract infection (URTI). The preliminary results are summarized in Figure 12 and Table 13 based on plasma-concentration vs. time curves and mean change in systolic blood pressure over time and summary of PK parameters. These results support that there was an insignificant impact on the pharmacokinetic or pharmacodynamic results from ***neffy*** 2 mg with natural infectious rhinitis conditions caused by a cold, flu, sinus infection or other viral infections. This study further supports that the EPI 16 study, where subjects were administered ***neffy*** 2 mg immediately after NAC induction of rhinitis, may be worst case conditions and that less impact on absorption would be observed with normal rhinitis conditions.

Figure 12: Plasma Concentration and Systolic Blood Pressure Change vs. time (EPI 14)



1.6.5. Clinical Safety

Overall, in all ***neffy*** studies there were approximately 600 subjects and over 1120 doses of product with both once and twice dosing.

The safety of ***neffy*** after single dose from the primary 2 mg studies (EPI 15, EPI 16, and EPI 17) demonstrate that more than 96% of adverse events (AEs) were mild, and no adverse reactions seen in greater than 10% of the subjects in any treatment group. The most common events were

nasal discomfort (9.7%), headache (6.0%), rhinorrhea (3.0%) nausea (2.2%) throat irritation (1.5%) and dizziness (1.5%). A total of 3 moderate events were observed in 1 subject with ***neffy*** 2 mg, which included vomiting, dizziness, and heart rate decrease. Two severe events were only observed in 1 subject in the EPI 17 study in allergy patients and included syncope and hypotension. In comparison, in the same EPI 17 study, there were 2 subjects with 3 severe events after treatment with 0.3 mg IM injection that included one each of syncope, asthenia, and blood pressure decrease. There were no serious adverse events (SAEs) in any ARS trials with ***neffy*** or injection products.

Twice dosing in the ARS primary studies with ***neffy*** 2 mg giving a total dose of 4 mg epinephrine in 10 minutes, resulted in 100% of events being mild and expected for epinephrine. There were no moderate or severe events with ***neffy*** 2 mg given twice. There was 1 moderate event in 1 subject with 0.3 mg IM given twice, which was vomiting.

Overall, the safety profile of ***neffy*** 2 mg was benign with >95% of events being mild common events and all events similar to IM injection. There was no dose related increase in adverse events with repeated doses of ***neffy*** 2 mg up to 4 mg.

1.6.5.1. Pediatric Population (≥30 kg)

Support for approval in pediatric Type I allergy patients ≥ 30 kg is provided based on pharmacokinetic data for the 2 mg dose of ***neffy*** in the ongoing EPI 10 study. The EPI 10 interim analysis in this briefing document, and filed to the NDA, assessed pharmacokinetic data on 57 children with severe Type I allergies at two doses including 16 children ≥ 30 kg treated with 2 mg ***neffy*** and 26 children ≥ 30 kg treated with 1 mg ***neffy*** (previous dose). Safety data from the EPI 10 studies consists of 77 children. There were two moderate TEAEs (nasal discomfort and sneezing) following administration of ***neffy*** 2 mg in one subject ≥ 30 kg. All other TEAEs were considered mild, and none were serious, life-threatening, or resulted in death.

Currently, the EPI 10 study is complete with the full 21 subjects enrolled in the 30 kg or greater body weight group with ***neffy*** 2 mg. Further, ARS has completed 21 subjects in the 15 to <30 kg group with ***neffy*** 1 mg dose and a supplemental NDA application is planned to be file for this lower dose and lower weight population if current application is approved.

1.7. Benefits/Risk of *neffy*

The pharmacokinetic data from the clinical pharmacology studies demonstrate that a 2 mg dose of ***neffy*** provided exposures that are bracketed by currently approved injection products (higher and more rapid exposures compared to 0.3 mg dose of epinephrine delivered by intramuscular (IM) administration and lower exposures than EpiPen 0.3 mg). When administered twice, ***neffy*** resulted in a dose proportional increase in epinephrine concentrations.

The pharmacodynamic results were mostly comparable between ***neffy*** and EpiPen despite the slightly higher and faster pharmacokinetic profile of EpiPen (Appendix 1). While the mean

increases in SBP are greater than that observed with injection, the maximum change in SBP in any individual subject is similar between treatments and there were no indications that the more rapid and greater mean pharmacodynamic effect poses any safety risk to patients experiencing a severe systemic allergic reaction. More likely, the efficient mean pharmacodynamic response of ***neffy*** may represent a potential improved effect based on time to onset, peak response, and a higher proportion of people having a positive hemodynamic response rapidly after administration. This effect may be especially relevant when a second dose is needed due to a more severe event (e.g., hypotension) or due to delayed treatment.

The anaphylaxis dog model demonstrated that during anaphylaxis conditions there was no negative impact of hypotension and other related allergic conditions on absorption of epinephrine from the ***neffy*** formulation dose intranasally with the same UDS device. The EPI 16 clinical study with NAC induced allergic rhinitis (congestion and rhinorrhea) demonstrated that epinephrine absorption is more rapid and greater than IM injection for at least the first 15 to 20 minutes after administration, which is when the efficacy of single dose epinephrine is observed (within 5-10 minutes). There was no meaningful impact of congestion associated with upper respiratory tract infections in the EPI 14 study.

neffy demonstrated an acceptable safety profile with events that were mostly mild and comparable to that of injection products.

Taken together, ***neffy*** 2 mg after single administration demonstrated comparable pharmacokinetic, pharmacodynamic, and safety profile to that of injection products and therefore patients and caregiver would benefit from this easy-to-use and needle-free option when they need emergency treatment. Twice dosing with ***neffy*** 2 mg resulted in dose proportional epinephrine exposure and greater pharmacodynamic effect then twice dosing with injection product, which is appropriate given a second dose is generally needed due to more severe events. The many patients and caregivers who cannot accept use of a needle-bearing device currently have no other treatment options. ***neffy*** can potentially fill that unmet medical need.

2. BACKGROUND

2.1. Overview of Serious Allergic Reaction Including Anaphylaxis

Anaphylaxis is the most severe form of allergic reaction, or hypersensitivity reaction, is almost always unexpected, and can be life-threatening (Tang-2009). The pathophysiology of anaphylaxis is primarily attributable to antigen-specific immunoglobulin E (IgE) activation and the subsequent activation of mast cells and basophils, ultimately leading to widespread release of histamine and other inflammatory mediators (e.g., cytokines). This histamine release results in generalized vasodilation, elevated heart rate, and increased vascular permeability (Peavy-2008), potentially leading to cardiovascular collapse.

Type I allergic reactions are potentially life-threatening hypersensitivity reactions that can occur within minutes of exposure to an allergen and generally require immediate treatment to relieve

symptoms and prevent further progression. If not treated immediately, the reaction can progress to a more severe stage known as anaphylaxis that involves constriction of the airways, swelling of the throat, rapid heart rate, severe hypotension and other respiratory and cardiac symptoms that can develop and potentially present a life-threatening emergency.

The Incidence of all-cause anaphylaxis in the United States has increased by 70% from 2004 to 2016. In 2016, the incidence rate was 218 per 100,000 persons in a patient population that was approximately 75% adults (Chaaban-2019).

Delay in treatment may result in death by airway obstruction or vascular collapse (Joint Task Force on Practice Parameters-2015). Overall rate of mortality from anaphylaxis in the United States is between 186 to 225 deaths per year (Ma 2013; Jerschow 2014). The vast majority of these deaths are persons that did not have epinephrine available at the time of the event or were not treated with epinephrine prior to emergency medical personnel could arrive (Poirot 2020).

2.2. Epinephrine's Mechanism of Action

Epinephrine is a non-specific adrenergic agonist that is the drug of choice for the treatment of severe allergic reactions and anaphylaxis. Its therapeutic efficacy comes from its direct agonism of α and β adrenergic receptors leading to a reversal of the pathological response to the histamine cascade.

2.2.1. Representative Epinephrine Receptor Activity

Immediate administration of epinephrine is currently the first-line treatment for severe Type I allergic reactions (Shaker-2020) including anaphylaxis. Epinephrine's MOA for the treatment of Type I allergic reactions and anaphylaxis is generally well understood and comes from direct systemic agonism of α- and β-adrenergic receptors, leading to a reversal of the pathological response to the histamine cascade caused by an antigen (Table 13).

Table 13: Main Pharmacologic Effects of Epinephrine

Adrenergic Receptor	Pharmacological Effect of Agonism by Epinephrine	Clinical Effect of Agonism by Epinephrine
α1	• Increases **blood pressure** • Decreases mucosal edema	• Relieves hypotension and shock • Relieves upper airway obstruction
β1	• Increases blood pressure and **heart rate**	• Relieves hypotension and shock
β2	• Relaxation of bronchial smooth muscles • Vasodilation in skeletal vasculature • Inhibits inflammatory mediator release from mast cells and basophils	• Increase in bronchial airway • Increases blood flow to skeletal muscle • Reverses pathological histamine cascade

The clinically observed responses of presenting anaphylaxis symptoms to initial epinephrine therapy include improved breathing, reduction in oedema, and reversal of rash, flushing and urticaria (Lindbeck-1995). These symptoms are easily observed by both patients and/or their caregivers, allowing for decisions regarding the need for a second dose (5 to 15 minutes following the initial dose, as per the epinephrine labeling). The response of these initial symptoms to epinephrine treatment is primarily attributable to the β_2 agonism described above and are the first effects observed given β_2 receptors high affinity for epinephrine.

Activation of β_2 receptors (which are located in the vessels of the skeletal muscles) can also result in vasodilation. Vasodilation decreases peripheral vascular resistance, resulting in increased blood flow to skeletal muscle. Diastolic blood pressure (DBP) can initially decrease after administration of epinephrine as a result of this increased blood flow, which may suppress SBP as well. However, as epinephrine plasma levels increase the α_1 receptor agonism increases and initiates a vasoconstrictive response that opposes the β_2-mediated vasodilation, ultimately resulting in an increase in blood pressure (Westfall-2011).

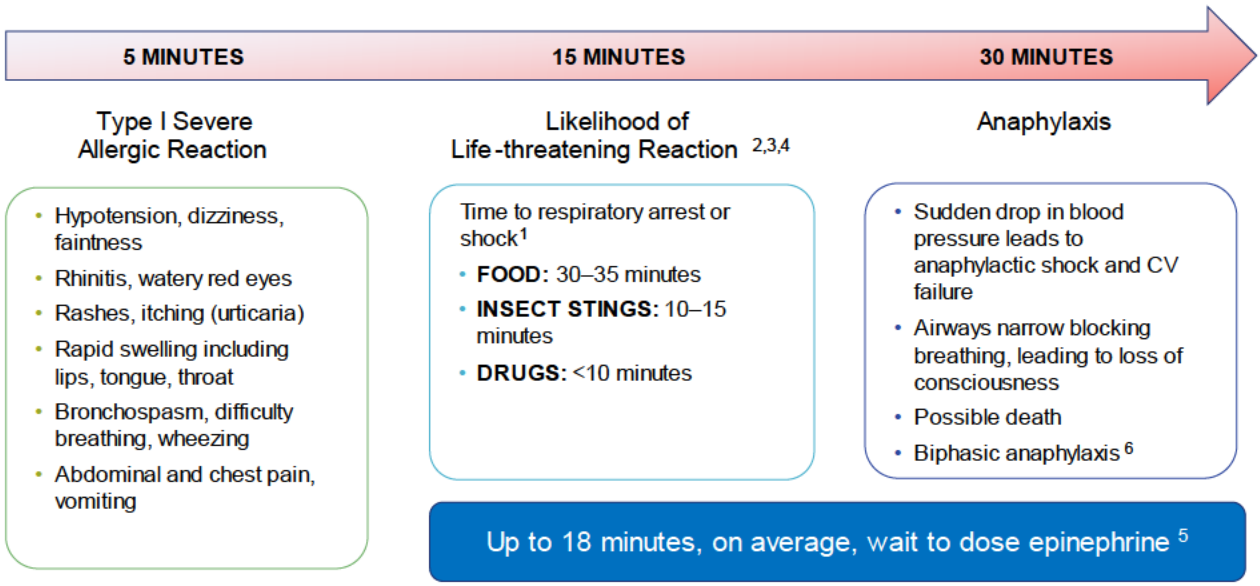
Epinephrine's ability to activate β_2 receptors explains why it is ideally suited for the treatment of anaphylaxis, while, in contrast, norepinephrine's lack of β_2 receptor stimulation makes it a more optimal drug to support blood pressure in shock, but less-than-ideal for the treatment of anaphylaxis.

2.2.2. Early Intervention with Epinephrine is Critical

Symptoms of a Type I allergic reaction (Figure 13) are often variable and it can be difficult to predict severity and rate of progression of an episode. Because the clinical course of anaphylaxis can be unpredictable, prompt, and early use of epinephrine should be considered even with mild

symptoms or single-system involvement (Shaker-2020). In the absence of clinical improvement, guidelines for the treatment of anaphylaxis recommend administering repeated doses of epinephrine every 5 to 15 minutes.

Figure 13: Early Intervention with Epinephrine – Time is Critical



1. Emergency treatment of anaphylactic reactions guidelines for healthcare providers. Resuscitation Council (UK) 2016 2. JF Philips et al. Allergy Asthma Proc (2011) 3. JT Fleming et al. J Allergy Clin Immunol Pract (2014) 4. E. Andrew et al. Prehospital Emergency Care (2018) 5. ARS market research 6. Liu 2020

2.3. Current Treatment Options

Epinephrine has been used for multiple indications for over 100 years and was approved for use in the US in 1939 for treatment of septic shock. The use of epinephrine for the treatment of anaphylaxis was first reported in the 1960s and was based on empiric observation and expert opinion (Simons-2006, Upton-2014). Epinephrine is the only first-line treatment for anaphylaxis and there are no absolute contraindications to its use.

There are several routes of epinephrine administration used for the treatment of severe allergic reactions and anaphylaxis including intravenous (IV) infusion, IV bolus, intramuscular (IM), and subcutaneous (SC) administration. While there are limited published pharmacokinetic (PK) data on these routes of administration in the literature, extensive clinical experiences support the safe and effective use of all approved routes of administration in the treatment of severe allergies including anaphylaxis. The US FDA has approved intramuscular and subcutaneous epinephrine injection and epinephrine autoinjectors including EpiPen Jr®, Auvi-Q®, Adrenaclick®, Symjepi™, and generic epinephrine autoinjectors (Table 14). With exception of Auvi-Q, there were no clinical trials, nor PK studies, conducted to support approval of currently approved community use injection products and all were based on the observed efficacy of IM injection (needle & syringe) used in clinical settings. More recently it has been established that the

different autoinjector products and manual IM injection with needle and syringe, all have very different pharmacokinetic profiles. Despite these differences the efficacy and clinical outcomes of such epinephrine products have been acceptable. All approved products in the treatment of severe allergic reactions including anaphylaxis are used interchangeably with same guidance– immediately dose and wait 5 to 15 minutes to observe clinical response, then give a second dose if no response.

Table 14: History of FDA Approved Community Use Products

Device (Approved)	Approval Basis	Pharmacokinetics (any data including literature)
EpiPen (1987)	No Clinical or PK Data	Significant differences (EpiPen vs. IM) only known in past ~10 yrs Significant blood vessel injection risk (IV bolus) only known last 5 yrs
Twinject (2003)	No Clinical or PK Data	No PK data known to date
Adrenaclick (2003)	No Clinical or PK Data	No PK data known to date
Auvi-Q (2012)	Single PK Study vs. EpiPen	More rapid PK vs. IM, but **slower PK vs. EpiPen** (t_{max} = 20 min vs. 10 min)
Symjepi (2017)	No Clinical or PK Data	ARS studies show **slower PK vs. *neffy* or other autoinjectors**
Teva Generic EpiPen (2018)	No Clinical or PK Data	None to date; shorter needle and different activation force

2.3.1. Dosages

Dosing in a community setting with auto-injectors or prefilled syringes is typically 0.3 mg injection for all persons 30 kg (0.01 mg/kg) and above. For children aged 6 years and older, with body weight of ≥15 kg, a 0.15 mg auto-injector dose is available for community use.

2.3.2. Efficacy of IM injection and EpiPen are Equivalent in Practice

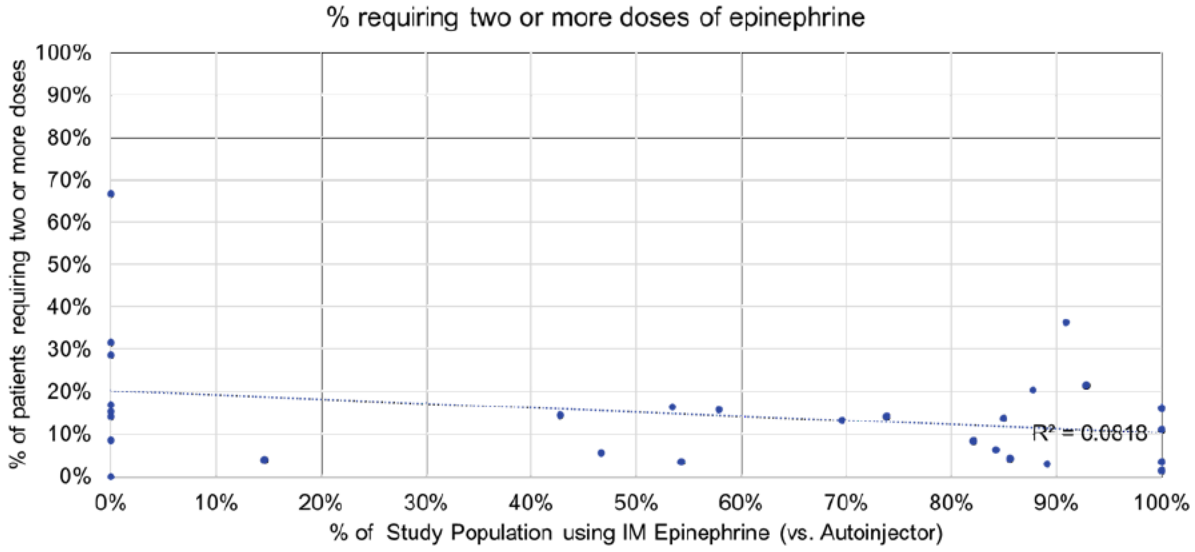
While controlled clinical trials have not been conducted with various epinephrine injection products, several studies have evaluated efficacy based on resolution of the allergic event after a single dose and the frequency with which a second dose was needed. Among the 21 studies that reported about second dose of epinephrine (Kahveci-2020, Oya-2020, Kondo-2018, Cardona-2017, Oren-2007, De Swert-2008, Johnson-2014, Nogic-2016, Grabenhenrich-2018, Campbell-2015b, Lee-2015, Ben Shoshan-2013, Soller-2019, White-2015, Arkwright-2009, Gold-2000,

Webb-2006, Noimark-2012, Cardona-2020) the weighted average for the rate of second injections from studies in which there was 100% use of one product shows that there was a slightly higher rate of second injections when EAIs were the predominant injection product (Table 15). Overall, there did not appear to be any relationship between the need for a second dose and the type of injection product used for the initial treatment ($r^2 = 0.0818$) (Figure 14).

Table 15: Weighted Average of Second Doses by Product, Based on Studies 100% Use of Either IM Needle/Syringe or Epinephrine Autoinjector

Product	Absolute Number of Events	Percent of Patients Requiring a Second Dose
Autoinjector	799	10.9
IM Needle/Syringe	570	9.3

Figure 14: Relationship Between the Use of IM Epinephrine vs. Autoinjector on Frequency of Second Dose



2.4. Unmet Medical Need

The importance of early epinephrine treatment has been emphasized in the literature, guidelines, and FDA approved product labeling (Fleming-2015, Sicherer-2017, Shaker 2020, Muraro-2021) for treatment of Type I allergic reactions and anaphylaxis.

It has been reported that delayed use of epinephrine has been associated with the following outcomes (Patel-2021; EpiPen Package Insert-2020; Hochstadter-2016; Andrew-2018; Liu-2020; Fleming-2015; Turner-2017).

- Increased epinephrine requirement to control anaphylaxis symptoms (OR = 5.0)
- Abnormal vital signs – heat rate, systolic blood pressure, respiratory rate ($p<0.001$)
- Biphasic anaphylaxis (OR = 3.4)
- Risk factor for hospitalization (HR = 4.0)
- Fatality

However, the Asthma and Allergy Foundation of America has reported that 72% of parents did not administer epinephrine to their child, even when they knew the child was experiencing a severe allergic reaction (Asthma and Allergy Foundation of America-2019). Noimark et al (Noimark-2012) reported that on a cohort of 969 pediatric allergy patients and found that 245 patients (25%) met the criteria for anaphylaxis over the course of one year. Of those 245 patients, 204 (83%) failed to treat the episode with epinephrine. When considering patients who present to the emergency department, it has been reported that one-third of patients do not receive epinephrine prior to presenting to the emergency department, even when their severe allergic reaction progressed to anaphylaxis (Brooks-2017, Fleming-2015).

The reasons for delayed epinephrine are primarily driven by fear of the needle (needle phobia), concerns about safety, complexity of the device and concerns about having to go to the emergency room (ER) after dosing, often resulting in hesitancy to use the devices, delayed treatment, and an increased risk of serious complications and hospitalizations (Sampson-1992; Søreide-1988; Pumphrey-2000, Casale-2022). Prince et al (Prince-2018) explored the barriers to epinephrine use by patients and caregivers which included fear of the needle injection, failure to carry the EAI, failure to recognize allergic reactions, lack of proper training regarding how to use EAIs and cost. Misconceptions included a belief that epinephrine should not be used in patients with a history of cardiovascular disease, a belief that EIAs cannot be used in infants, a belief that EAIs are harmful, and a belief that one must go to the emergency department following epinephrine use, which is implied in current product labeling. Uncertainty regarding whether or not the reaction was severe enough to warrant treatment and/or a belief that epinephrine was not necessary being among the most commonly cited reasons (Asthma and Allergy Foundation of America-2019, Noimark-2012, Warren-2018). Other cited reasons for delayed epinephrine administration included fear of a “bad outcome or death” (Chad-2013); a failure to recognize the allergic reaction, epinephrine was unavailable (Fleischer-2012); and uncertainty regarding how to use EAIs (Warren-2018). The most common concerns contributing to not having epinephrine present at all or dosing delays in an allergy emergency are listed in Table 16.

Table 16: Unmet Needs and Product Attributes to Address

Reasons for delaying or not administering epinephrine		Product attributes needed
Never filling prescription	Of the 5.5 million prescriptions written approximately 43% are never filled (Cohen 2021, IQVIA Claims Data 2022) primarily due to needle-phobia, portability and complexity of the devices.	Smaller, needle-free, pain-free, easier to use devices
Lack of carriage	Due to their large size, injection devices typically lack ease of portability with less than 50% of patients and caregivers reporting that they are carrying one device when an allergic reaction occurred, <10% carry two devices (Warren-2018)	Smaller more portable devices
Fear of the needle	Needle phobia is the primary cause for failure to administer (25%-50% of events) or delayed treatment (until more severe and up to 18 minutes in studies) with epinephrine when needed (Noimark-2012; Fleming-2015; Brooks-2017)	Needle-free, pain-free
Concerns about safety	Injection products are associated with a range of safety concerns, including lacerations, injection into the bone, injection into blood vessels (IV bolus administration) and accidental patient or caregiver self-injection into an extremity (e.g., hand) (Anshien-2019; Guerlain-2011; ARS clinical studies; El Turki-2017; Moss-2018; FDA-2015; 2017; 2020; 2022; Brown-2016; Kim-2017, Ebisawa-2022). Additionally, there are reports of frequent and potentially cardiotoxic blood vessel injections, which occurred in approximately 14% of EpiPen subjects (N = 162) based on ARS clinical trials (Lockey-2022).	Needle-free, Patient education
Complex administration	23 to 35% error rate after training; Multiple device reliability recalls/warnings by FDA (El Turki-2017; FDA-2015; 2017; 2020; 2022)	Easy to use device, Rapid to administer, intuitive to use devices, Reliable
Uncertainty if symptoms warrant use	Wait until disease progresses to a severe state	Patient education regarding safety of epinephrine, Needle-free, pain-free device
Availability	Epinephrine not available in public locations due to injection related risks	Needle-free; intuitive to use devices

As a result of these limitations, a significant proportion of the approximate 40 million patients at risk of severe Type I allergic reactions in the United States do not receive or fill prescriptions for

intramuscular injection products, such as EpiPen or generic equivalents. Of the 3.3 million patients who fill their prescriptions in the US, fewer than half carry the intramuscular injectable products with them on a regular basis, while many of the other half delay treatment during a severe type I allergic reaction (Brooks-2017; Fleming-2015). This hesitancy results in the prolonging troublesome symptoms and an increased risk of progression of the reaction to anaphylaxis, including possible long-term comorbidities or even death (Warren-2018).

Therefore, there is a significant unmet need to address these issues as many patients and caregivers are unwilling to use a needle-bearing device. ***neffy*** has the potential to address many of these unmet medical needs as needle-free option to current injection devices.

2.5. *neffy* Product Features

With its needleless design and ease of use, ***neffy*** addresses several key concerns, both with regard to safety and hesitancy to dose. As part of the research study described above, ARS asked participants to rate (on a scale of 1 – 10) what feature would motivate them to use ***neffy*** sooner than their current device (Table 17). Ease of use was the most highly rated feature that participants anticipated would reduce hesitancy, followed by less pain, no needle, reduced fear of striking bone, and reduced fear of cardiovascular side effects.

Table 17: Features Anticipated to Contribute to More Rapid Use of *neffy* vs EAIs

Feature	Mean Score (scale of 1 – 10)		
	Self-Administered (n = 100)	Caregiver Administered (n = 100)	Total (n = 200)
Easier to use / Less complicated to use	8.3	8.4	8.4
Less pain upon use	7.7	8.2	7.9
No needle	7.6	8.1	7.8
Eliminates fear of causing harm due to lacerations or striking bone rather than muscle	7.7	7.9	7.8
Lessens fear of causing harm due to cardiovascular complications, or epinephrine overdose	7.5	8.0	7.7
Easier to carry / Portability	7.4	7.4	7.4
Smaller size	7.1	7.0	7.1

Both the published literature (Boswell-2021) and the ARS questionnaire results in patients and caregivers with recent experience dosing epinephrine injection devices (within 1 year) suggests that there are gaps in the current treatment of severe allergic reactions and anaphylaxis, and that these treatment gaps are largely driven by a reluctance to utilize current therapies. Understanding and addressing these barriers is crucial to providing a quality therapeutic product. With its needleless design and ease of use, ***neffy*** addresses several of documented concerns, however further work needs to be done to educate patients regarding the safety and efficacy of

epinephrine products for the treatment of severe allergic reactions and anaphylaxis, as well as how and when these products should be used.

In addition to addressing the issues surrounding hesitation to dose, ***neffy's*** needleless design also completely eliminates the risks of accidental intra-vessel administration observed with EAIs.

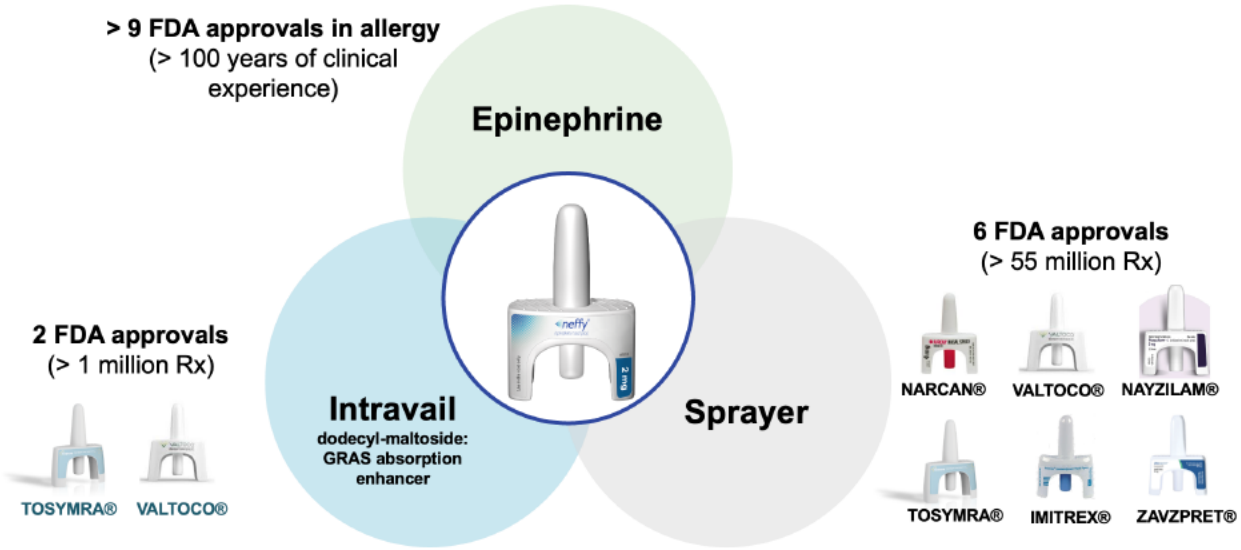
3. *neffy* PRODUCT DESCRIPTION

neffy (epinephrine nasal spray) is a combination of three previously validated product components (Figure 15), including:

1. Epinephrine
2. a proprietary absorption enhancing agent called dodecylmaltoside (DDM) to improve the bioavailability of drugs administered by the intranasal (IN) route
3. a commercial Unit Dose Sprayer (UDS) that is designed to produce a spray pattern and droplet size that maximizes the delivery to the turbinates

Once administered, epinephrine is primarily absorbed into the systemic circulation rapidly via the highly vascularized turbinates (Kapoor-2016)

Figure 15: *neffy* Triad



3.1. Epinephrine

Epinephrine has been used for more than 100 years, with more than 60 years use to treat severe allergic reactions, and there has been extensive clinical experience with the use of epinephrine to

treat anaphylaxis, severe allergy such as asthma, and shock. The use of epinephrine for the treatment of anaphylaxis is supported by both pharmacologic and physiologic experiments in multiple animal studies, as well as reports from clinical experiences. Its use has been adopted as the standard-of-care, first-line treatment of anaphylaxis (Lieberman-2015, Simons-2011).

3.2. Dodecylmaltoside (DDM)

neffy is a formulation of epinephrine that includes a proprietary functional excipient called dodecylmaltoside (DDM), supplied and licensed by Aegis Therapeutics. DDM is an approved excipient in the United States, used to improve the bioavailability of drugs administered by the intranasal (IN) route. DDM loosen cell-cell junctions and enhance paracellular movement through the nasal epithelium, behaving as a permeation enhancer when combined with certain medications intended for intranasal administration (Lipton-2018, Munjal- 2017, Hogan-2020, Maggio-2014).

The ***neffy*** (epinephrine) nasal spray formulation was found in Phase 1 studies to have an optimal bioavailability with the addition of 0.275% DDM. DDM has been included in the formulations of FDA approved products, such as VALTOCO® nasal spray and TOSYMRA® nasal spray and there have been no safety issues reported.

3.3. Unit Dose Sprayer (UDS)

The UDS device used for ***neffy*** is well known and proven and has a 20-year history of use with no recalls. It is a single dose device that does not require any priming or other activation. It is a simple to use mechanism that is highly reliable, with less than 1 in 100,000 chances of a failure and delivers an effective dose within specifications based on reliability testing for ***neffy*** and other products using the UDS device. In addition to the real-world experience with this device ARS has conducted multiple reliability studies with the ***neffy*** 1 mg and ***neffy*** 2 mg products. The intranasal UDS device used has been commercially proven with millions of sprayers sold across multiple FDA-approved products, including NARCAN® for opioid overdose with 50 million subscribed since 2015 and VALTOCO® nasal spray for epilepsy, as well as other approved products (Figure 15).

3.4. Nasal Absorption of Epinephrine

Due to their large surface-to-volume ratio, the highly vascularized turbinates, which are small structures within the nose that cleanse and humidify air that passes through the nostrils into the lungs, have the ability to rapidly absorbed intranasally delivered drugs into the systemic circulation. Indeed, the nasal turbinates are the primary sites of absorption of intranasally delivered drugs (Kapoor-2016). The primary factor in the fluid dynamics of a nasal spray is the droplet size and droplet sizes of less than 10 µm are required to penetrate past the nasopharynx (Calmet-2019, Frank-2012). Above 10 µm droplet size, Frank et. al. (Frank-2012) predicts that nearly 100% of the spray is deposited in the nasal cavity (i.e., anterior region and turbinates). Droplets in the 20 µm to 120 µm size are almost exclusively captured on the terminates and the

design of the Unit Dose sprayer ensures that more than 80% of the total droplets are in this range.

4. CLINICAL DEVELOPMENT PROGRAM AND RATIONALE

neffy's clinical development program is centered on pharmacokinetic and pharmacodynamic data, as randomized clinical trials in patients in patients experiencing an anaphylactic reaction are considered unethical:

1. Bracket approach: the rationale that a single dose of ***neffy*** 2 mg has a pharmacokinetic profile that is similar to other injection products and bracketed by EpiPen 0.3 mg and Epinephrine 0.3 mg IM (discussed in Sections 4.1 and 4.2) with other approved injection devices also within this bracket; and

2. The use of pharmacodynamic data is a surrogate for efficacy (discussed in Section 4.3).

3. With repeat dose of ***neffy*** 2 mg a pharmacokinetic profile greater than injection products is warranted given the more serious nature of the disease including hypotension. ***neffy*** 2 mg is dose proportional with repeat dosing and between doses, while injection products have been proven to not be dose proportional. This results in a more consistent and better epinephrine exposure and pharmacodynamic response with ***neffy*** 2 mg versus twice dosing of approved injection products.

4.1. Pharmacokinetic Variability of Epinephrine Injection Products

Approved epinephrine injection products have been shown to be highly variable from study to study (Figure 16) (Lockey-2022, Turner-2022) with a median T_{max} values ranging from 5 to 60 minutes and mean maximum concentration (C_{max}) values ranging from 209 to 869 pg/mL (Table 18).

While each injection product has a notably different pharmacokinetic profile, they are used interchangeably with same guidance. All injection products typically demonstrate therapeutic effects within 5 to 10 minutes after administration, with instructions to administer a second dose if symptoms are not alleviated within 5 to 15 minutes if clinical benefit is not observed.

Figure 16: Variable Pharmacokinetic Profiles of Epinephrine Injection from ARS Studies

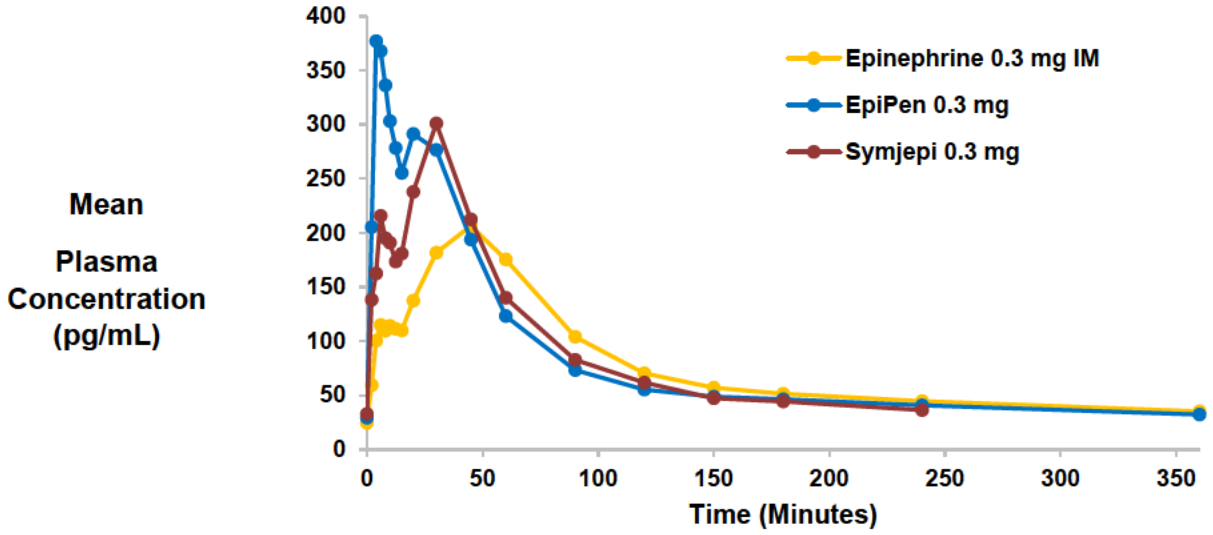


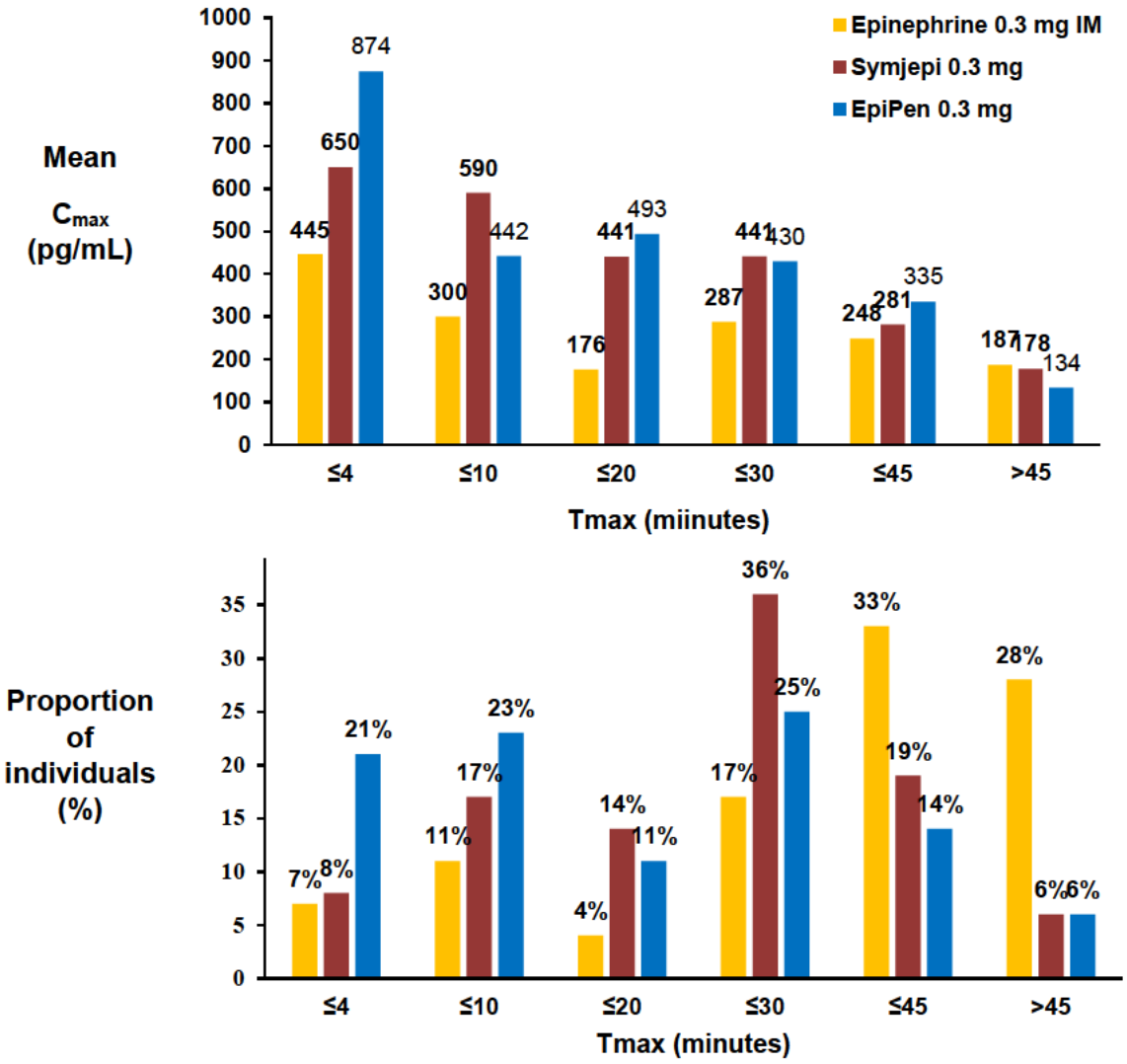
Table 18: PK Parameters Across Injection Products

Treatment*	Source	N	Mean Study C_{max} (pg/mL)	Median or Mean Study T_{max} (min)	Study T_{max} Range (min) in individuals
Epinephrine 0.3 mg IM	Literature	200	209 - 489	30 - 60	3 - 120
	ARS*	223	244 - 339	45	3.9 - 360
Symjepi 0.3 mg	ARS*	36	438	30	4- 360
Auvi-Q 0.3 mg**	Literature	67	486	20	5 - 60
EpiPen 0.3 mg	Literature	311	288 - 869	5 - 40	1 -120
	ARS*	113	375 - 753	7.5 - 24	2 - 154
Total Range			**209 - 869**	**5 - 60**	**1 - 360**

*ARS data = EPI 03, 04, 07, 12, 15, 16, and 17 Studies; **Baseline corrected
Note: no literature data are available for Twinject or Adrenaclick

To further explore the observed differences in C_{max} and T_{max}, we analyzed T_{max} at discrete intervals over time (≤4, >4 – ≤10, >10 – ≤20, >20 – ≤30, >30 – ≤45, and >45 minutes, presented as ≤4, ≤10, ≤20, ≤30, ≤45, and >45 minutes, respectively) (Figure 17). C_{max} increased when the T_{max} was faster with EpiPen having the greatest increase in T_{max} ≤4. EpiPen was associated with the greatest likelihood of a faster T_{max}, with 21% of individuals in this group exhibiting a T_{max} of ≤4 minutes with 23% and 25% in ≤10 and ≤30, while there is a tendency to have peak proportion of individual around 45 minutes with IM injection and 30 min with Symjepi.

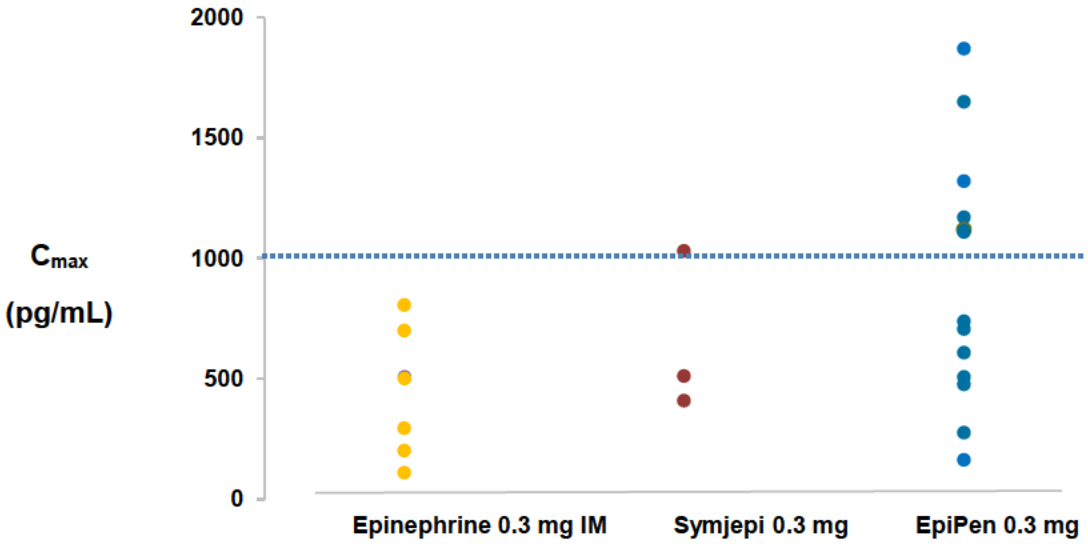
Figure 17: Mean C_{max} (top) and Distribution of Individuals (bottom) Across T_{max} Categories



Source: EPI 03, 04, 07, and 12 Studies

The C_{max} distribution for individuals with T_{max} ≤4 min suggests that the greater mean C_{max} observed with EpiPen 0.3 mg in this T_{max} category was likely driven by the proportion of individuals with a C_{max} >1000 pg/mL (Figure 18).

Figure 18: Distribution of Cmax values of individual participant with Tmax ≤4 minutes



Source: EPI 03, 04, 07, and 12 Studies

Individual epinephrine concentration over time curves were assessed for all individuals who had plasma epinephrine concentration >1000 pg/mL within ≤4 minutes of injection (Figure 19). Figure 20 represents the time course of epinephrine concentration and SBP with a subject (101) with presumed intra-blood vessel administration (IV bolus injection) via EpiPen and the rest of the subjects in EPI JP01 study. These curves exhibited an immediate sharp peak, suggesting some degree of intra-blood vessel administration.

Figure 19: Epinephrine concentration versus time for individual participants reaching plasma epinephrine concentrations of >1000 pg/mL with Tmax ≤4 min

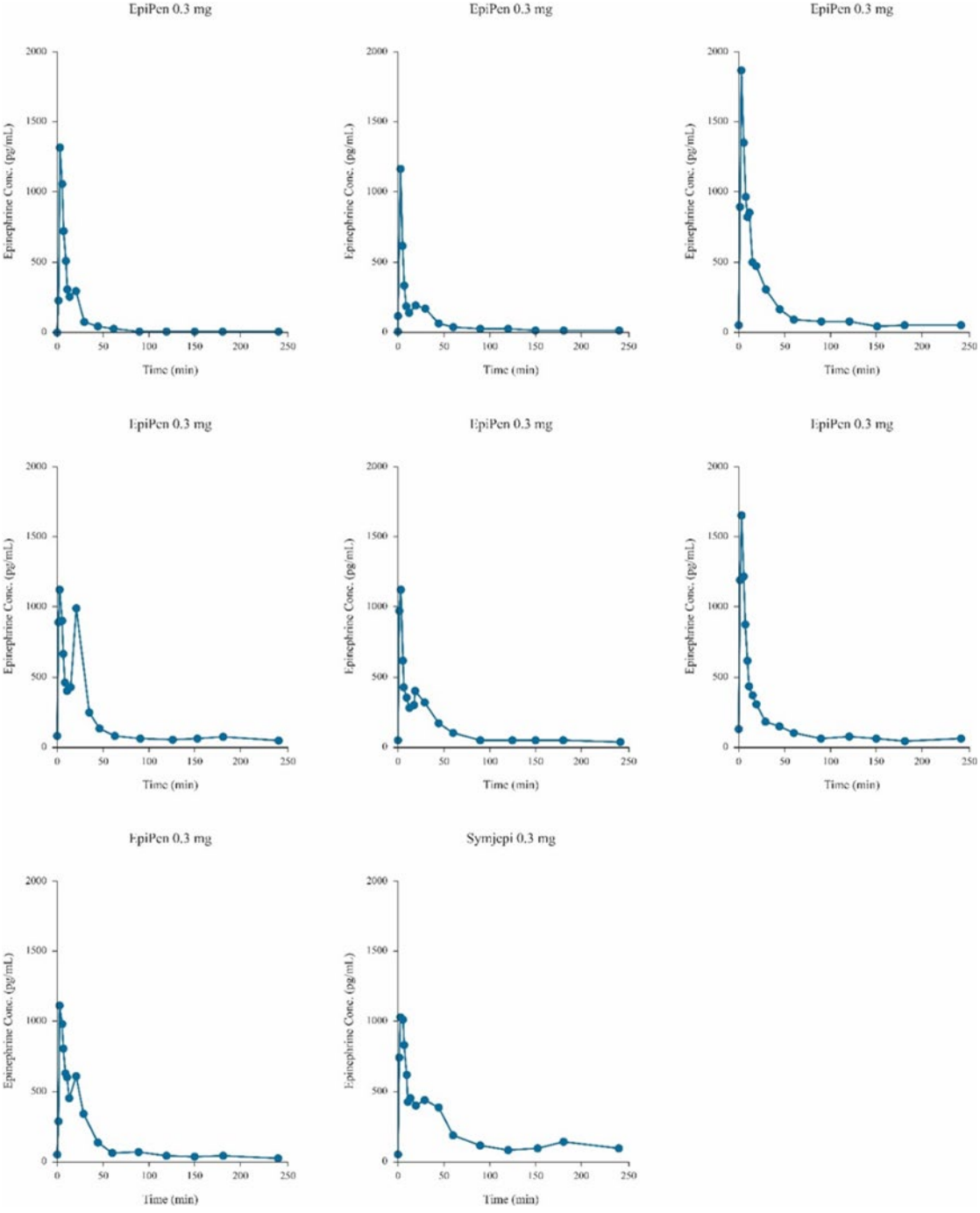
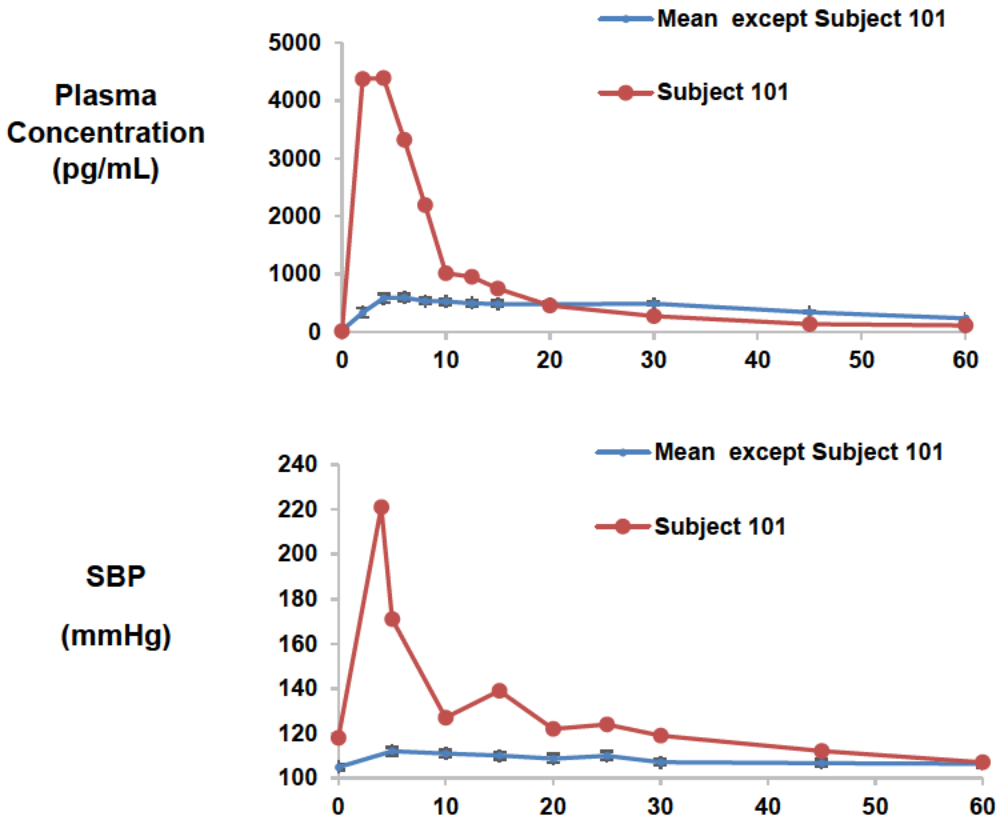
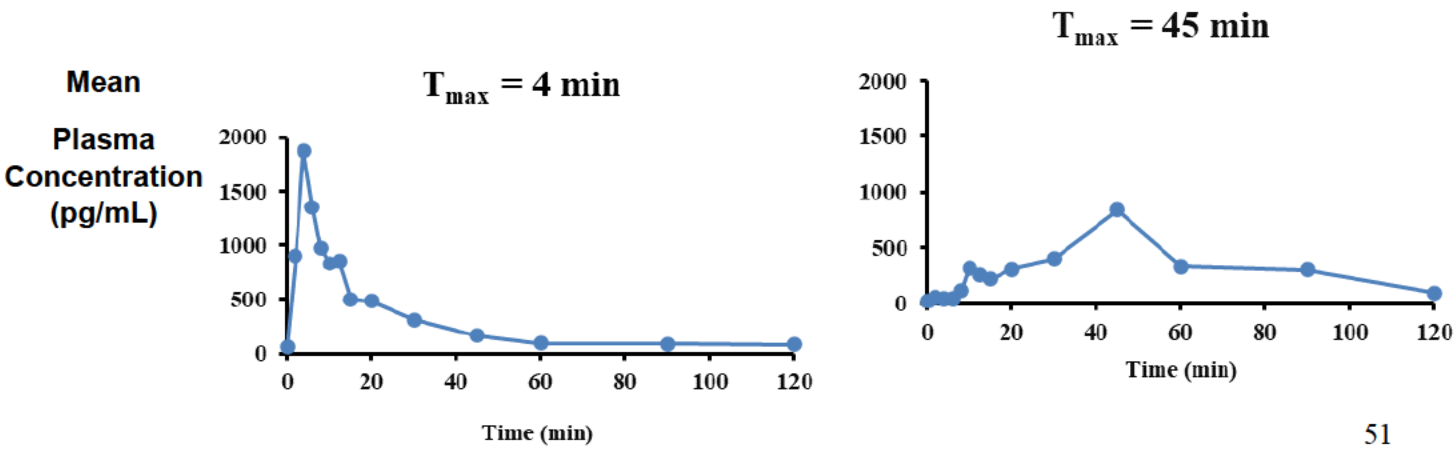


Figure 20: Time Course of Pharmacokinetic and Pharmacodynamic (SBP) Responses After Administration of Epinephrine via EpiPen



Based on the integrated analysis, the PK profile of injection products are most likely a mixture of a subset of early peak with some influence from intra-blood vessel administration (Figure 17), like intravenous, and a subset of later peak, which may be truly intramuscular injections (Figure 21).

Figure 21: Early and Late Peaks following Injection



Since it appeared that the PK profile of injections are a mixture of IM-like and IV-like PK and all injections products are used interchangeably, our approach for the assessment was to have neffy within the range or bracket of approved products.

4.2. Bracketing Approach

While IM injection (needle and syringe) is the basis for epinephrine efficacy and the lower end of the PK range for injection products and EpiPen (Autoinjector) is the higher end of PK range for injection products with study-to-study variability, all FDA approved injection products give similar efficacy and acceptable safety profiles (90% effective with a single dose).

Therefore, EpiPen and Epinephrine 0.3 mg IM were chosen as comparators for the following reasons:

- Epinephrine 0.3 mg IM is at the low end of the pharmacokinetic range for epinephrine injection products and is the standard by which epinephrine efficacy is measured.
- EpiPen is at the high end of the pharmacokinetic range for epinephrine injection products and, as such, serves as a standard by which safety is measured.

A bracketing approach (Table 19), in agreement with FDA and as described above, was used to demonstrate pharmacokinetics within the range of that known to be efficacious and safe. IM injection (needle and syringe) was selected as the reference for efficacy with ***neffy*** pharmacokinetics being greater and more rapid than IM. EpiPen, while highly variable from study to study (Appendix 1), exhibits the highest exposures and most rapid T_{max} and was used as the upper reference in the bracket to ensure exposures were in a safe range.

Table 19: Bracket Approach for Pharmacokinetics

Bracketing Criteria	Lower Bracket	Upper Bracket
C_{max} (primary)	0.3 mg IM	0.3 mg EpiPen
T_{max} (primary)	0.3 mg IM	0.3 mg EpiPen
$pAUC_{0\text{-}20,\ 0\text{-}30,\ 0\text{-}45}$ (primary)	0.3 mg IM	0.3 mg EpiPen
$AUC_{0\text{-}t}$ (secondary)		0.5 mg IM

4.3. Pharmacodynamic Data as a Surrogate for Efficacy

Randomized, controlled clinical studies of the treatment of patients at risk of anaphylaxis are unethical and/or impractical and no such comparative efficacy study with epinephrine has ever been conducted in patients at risk of serious allergic reactions and anaphylaxis.

There are several factors driving the lack of such studies. First, it is often impossible predict when and whether an allergic episode will progress to anaphylaxis, and the clinical course of allergic reactions can be unpredictable. Involvement of body organ systems in anaphylaxis

varies among patients even in the same patient from one allergic reaction to another. Such unpredictability of clinical course could put patients at risk of a life-threatening, potentially fatal condition. Second, given the high degree of variability in severe allergic reactions (type of allergen, treatments provided, etc.) a large study population would be required in order to achieve sufficient statistical validity, something that is a particularly large practical barrier given the relative infrequency of anaphylaxis. Third, adrenaline has been accepted as a treatment for anaphylaxis for over 100 years with various routes of administration and it is doubtful whether there is sufficient equipoise to support such a trial.

Additionally, epinephrine's MOA for the treatment of Type I allergic reactions and anaphylaxis is generally well understood and comes from direct systemic agonism of α- and β-adrenergic receptors, leading to a reversal of the pathological response to the histamine cascade caused by an antigen (Table 13).

Therefore, in collaboration with the FDA, PD endpoints were used as surrogate markers for efficacy, with the understanding that these endpoints (blood pressure and heart rate) are indicative of α- and β-adrenergic receptor activation and, consequently, clinical efficacy. Throughout the clinical development program, ***neffy***'s efficacy and safety has been established based on a series of clinical studies in both healthy volunteers and allergy patients.

4.4. Evaluation of Various Dosing Conditions

Because both ethical and practical limitations preclude the conduct of clinical trials in patients experiencing severe allergic reactions and anaphylaxis. Therefore, ARS conducted a GLP study using a dog anaphylaxis model to assess absorption during acute anaphylaxis. Further, ARS conducted two clinical trials to assess the pharmacokinetics and pharmacodynamics of ***neffy*** in subjects with allergic rhinitis (EPI 16) and upper respiratory tract infections (EPI 14) in order to evaluate the effect of nasal edema and congestion on the absorption of epinephrine administered via ***neffy***.

4.5. Summary of Completed ARS Clinical Studies

Based on FDA advice, ARS conducted four primary clinical pharmacology studies for approval of ***neffy*** 2 mg in adults and pediatric Type I allergy patients 30 kg or greater (EPI 10, EPI 15, EPI 16, and EPI 17). These studies support that ***neffy*** 2 mg will have PK parameters (C_{max}, t_{max}, AUC_{0-20}, AUC_{0-45}, and AUC0-t_l) within the range of US approved injection products during caregiver administration, self-administration and in various situations such as during rhinitis with rhinorrhea while in an upright sitting position. The primary four clinical pharmacology studies are supported by five large clinical studies that utilize the commercial ***neffy*** 1 mg product in adult Type I allergy patients (EPI 04 and EPI JP01), healthy volunteers (EPI 03 and 07), and with self-administration by Type I allergy patients (EPI 12). ARS started the development program with ***neffy*** 1 mg, which was similar to 0.3 mg IM injection. Subsequently, given the PK range of community-use injection products, ARS decided to increase the dose to 2 mg considering its out of hospital use. A summary of the primary and supportive studies is presented in Table 20. Five

additional studies pilot supportive studies or non-supportive for approval studies were also conducted.

Additionally, ARS has also conducted integrated pharmacokinetic-pharmacodynamic analyses, including Population Pharmacokinetic assessments (POP PK) and Physiologically Based Absorption Model (PBAM) to evaluate the data and extrapolate the pharmacokinetics and pharmacodynamics to other populations including children down to age 4 years. These models support that ***neffy*** should be safe and effective, giving exposures to epinephrine in the expected therapeutic range, in both adults and children aged 4 years and older.

Phase 2 studies with urticaria and asthma patients are ongoing.

Table 20: Summary of Primary and Supportive Clinical Pharmacology Studies

Study Number	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Population (Number)
neffy 2 mg Primary Studies Supporting Approval				
EPI 15	To assess the PK and PD of ***neffy*** dosed once and twice, compared to a single and repeat doses of IM epinephrine injection and EpiPen	Phase 1, two part, randomized, single-dose (3-treatment, 3-period) and repeat-dose (3-treatment, 3-period), crossover study	***neffy*** 2 mg IN ***neffy*** 2 mg IN, twice (R/L) ***neffy*** 2 mg IN, twice (R/R) Epinephrine 0.3 mg IM EpiPen 0.3 mg EpiPen 0.3 mg, twice	Healthy subjects (54)
EPI 16	To assess the comparative bioavailability of ***neffy*** dosed once to evaluate the impact of nasal oedema and congestion; compared to 0.3 mg and 0.5 mg IM.	Phase 1, randomized, single-dose, 3-treatment, 3-period, crossover study, followed by administration with induced rhinitis	***neffy*** 2 mg IN, normal conditions ***neffy*** 2 mg IN, rhinitis Epinephrine 0.3 mg IM Epinephrine 0.5 mg IM	Allergy Patients (36)
EPI 17	To assess the PK and PD of ***neffy*** as well as error rate following self-administration as compared to 0.3 mg IM injection	Phase 1, randomized, single-dose, 2-treatment, 2-period, crossover study	***neffy*** 2 mg IN, self-admin. Epinephrine 0.3 mg IM	Type I Allergy Patients (42)
EPI 10	To assess the PK and PD of ***neffy*** dosed once in pediatric allergy subjects (15-<30 kg; and 30+ kg body weight; age 4 to 17 years)	Phase 1, single-dose, single-treatment	***neffy*** 0.65 mg IN (15-30 kg) ***neffy*** 1 mg IN (15-30 kg) ***neffy*** 1 mg IN (≥30 kg) ***neffy*** 2 mg IN (≥30 kg)	Pediatric Type I Allergy Patients (57)

Study Number	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Population (Number)
neffy 1 mg and Dose Ranging Supportive Studies				
EPI 03	To assess the PK and PD of ***neffy*** dosed once and twice, compared to a single and repeat doses of IM epinephrine injection; Continuous EKG	Phase 1, randomized, single-dose, 5-treatment, 5-period, crossover study	***neffy*** 1 mg IN ***neffy*** 1 mg IN, twice Epinephrine 0.3 mg IM Epinephrine 0.3 mg IM, twice Epinephrine 0.5 mg IM	Healthy subjects (70)
EPI 04	To assess the comparative bioavailability of ***neffy*** dosed once to evaluate the impact of nasal oedema and congestion; compared to IM and SC.	Phase 1, randomized, single-dose, 5-period, partial cross-over study	***neffy*** 1 mg IN ***neffy*** 1 mg IN, w/ rhinitis Epinephrine 0.3 mg IM Epinephrine 0.5 mg IM Epinephrine 0.3 mg SC	Allergy Patients (36)
EPI 07	To assess the PK and PD of ***neffy*** dosed once and twice compared with EpiPen dosed once and twice.	Phase 1, randomized, 5-treatment, 5-period, crossover study	***neffy*** 1 mg IN (L nostril) ***neffy*** 1 mg IN, twice (L/R) ***neffy*** 1 mg IN, twice (L/L) EpiPen 0.3 mg (L thigh) EpiPen 0.3 mg, twice (L/R)	Healthy subjects (36)
EPI 12	To assess the PK and PD of ***neffy*** as well as error rate following self-administration	Phase 1 randomized, four treatment crossover study	***neffy*** mg; 0.25% DDM ***neffy*** mg; 0.35% DDM EpiPen (0.3 mg) Symjepi (0.3 mg)	Healthy subjects (36)
JP 01	To assess the PK and PD of ***neffy*** dosed once to evaluate the impact of nasal oedema and congestion; compared to IM and EpiPen in Japanese subjects.	Phase 1, partially randomized, four-treatment study	***neffy*** 1 mg IN Epinephrine 0.3 mg IM EpiPen 0.3 mg IM/SC ***neffy*** 1 mg IN, with rhinitis	Type I Allergy Patients (36)

Abbreviations: IM=intramuscular, IN=intranasal, PK=pharmacokinetic, SC=subcutaneous R/L=right/left R/R=right/right, L/R=left/right, L/L=left/left

5. RESULTS: OVERVIEW OF CLINICAL PHARMACOLOGY

ARS conducted four primary clinical pharmacology studies to demonstrate ***neffy***'s pharmacokinetic, pharmacodynamic, and safety profiles (Section 4.5). In each of these studies, pharmacodynamic responses were used as surrogate markers for efficacy. An integrated pharmacokinetic analysis was conducted using data from five randomized, open-label, single-dose phase 1 trials (EPI 03, EPI 04, EPI 07, EPI 15, and EPI 16). Some key data from EPI 17 (self-administration) and EPI 10 (pediatric patients) are also included in this section.

The following data are presented in this section:

- Overall PK of once- and twice-dosed treatments (Section 5.1)
- Overall PD of once- and twice-dosed treatments (Section 5.2)
- PK and PD in pediatric patients (Section 5.3)
- PK and PD of Various dosing conditions (Section 5.4)

5.1. Integrated Pharmacokinetic Results

When administered once, the pharmacokinetic profile of ***neffy*** 2 mg was bracketed by approved injection products. ***neffy*** demonstrated greater and more rapid exposure compared to Epinephrine 0.3 mg IM (the RLD drug for efficacy) and a lower C_{max} and more controlled absorption relative to EpiPen (the upper limit for safety) (Figure 21).

When administered twice, ***neffy*** resulted in a dose proportional increase in epinephrine concentrations (Figure 24). Following two administrations ten minutes apart, ***neffy's*** C_{max} following twice dosing was 196% (R/L) and 202% (R/R) and ***neffy's*** AUC_{0-45} was 184% (L/R) and 193% (R/R) of a single dose. In contrast, the IM injection products did not result in dose proportional increases, with twice dosing resulting in a C_{max} of 165% and an AUC_{0-45} of 154% of a single dose. The lack of dose proportionality seen following IM injection is likely due to the increased blood flow into the skeletal muscle in the thigh that is more prominent following the first injection by IM injection (Tanimoto-2022).

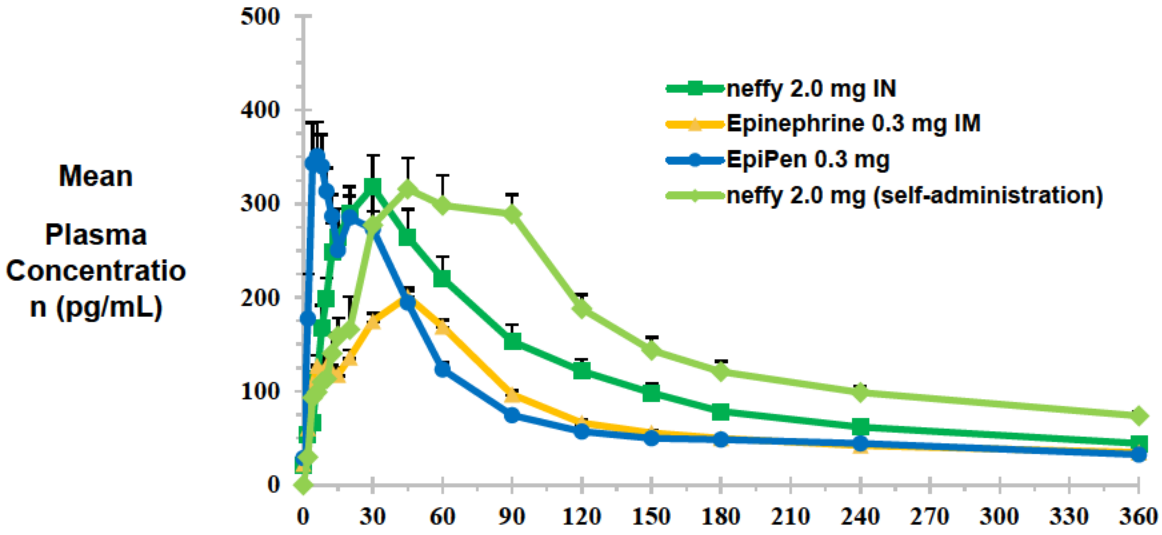
neffy's dose proportionality may be particularly advantageous during more severe Type 1 allergic reactions, when a second dose is necessary to achieve an acceptable therapeutic effect.

5.1.1. Pharmacokinetics of Once Dosed Treatments

Mean by-treatment (once dosed) plasma concentration vs time profiles are presented in Figure 21 and that of self-administration is presented in Figure 22. Pharmacokinetic parameters are presented in Table 21.

neffy's pharmacokinetic profiles were bracketed by EpiPen (at the upper end) and Epinephrine IM 0.3 mg (at the lower end).

Figure 22: Plasma Concentration vs Time Profiles of Epinephrine, Once Dosed, by Treatment



Statistical significance
neffy 2.0 mg vs. Epinephrine 0.3 mg IM: 8 to 360 min ($p<.01$), 4 min ($p<.05$)
neffy 2.0 mg vs. EpiPen 0.3 mg: 2 to 10 min and 45 to 240 min ($p<.01$), 360 min ($p<.05$)

Table 21: Summary Statistics of Total Epinephrine Pharmacokinetic Parameters - Once-Dosed Treatments

Product	N	C_{max}	T_{max}	$pAUC_{0-20}$	$pAUC_{0-45}$	AUC_{0-t}
		(pg/mL) Mean (CV%)	(minutes) Median (range)	(min*pg/mL) Mean (CV%)		
Epinephrine 0.3 mg IM	178	277 (65)	45 (4-360)	2090 (86)	6290 (61)	27900 (39)
***neffy* 2 mg (self-administration)**	**42**	**421 (66)**	**30 (6-240)**	**2964 (71)**	**10545 (63)**	**46776 (56)**
***neffy* 2 mg**	**78**	**485 (71)**	**20.5 (2-150)**	**3610 (84)**	**11000 (76)**	**40900 (68)**
EpiPen 0.3 mg	77	581 (76)	10 (2-45)	5640 (73)	12000 (53)	31600 (39)

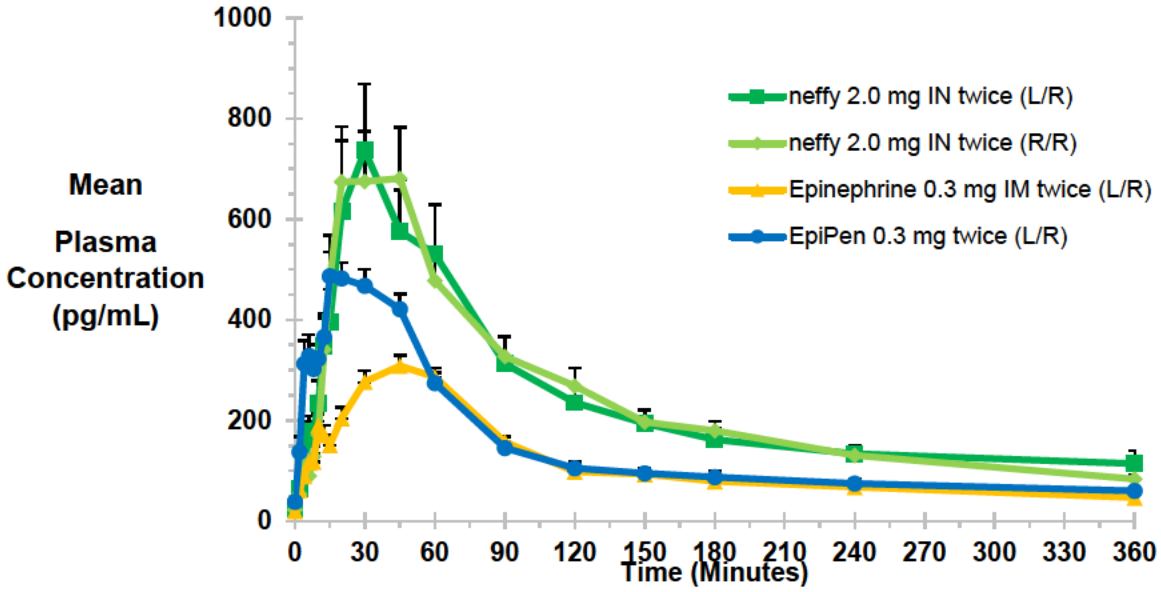
* EPI 17 Study; Note: mean AUC0-t of Epinephrine 0.5 mg was 43700 min*pg/mL
Statistical significance
neffy 2.0 mg vs. Epinephrine 0.3 mg IM: Cmax, $pAUC_{0-20}$, $pAUC_{0-45}$, AUC_{0-t} ($p<.01$)
neffy 2.0 mg vs. EpiPen 0.3 mg: pAUC0-20, AUC_{0-t} ($p<.01$)

5.1.2. Pharmacokinetics of Twice Dosed Treatments

Mean by-treatment (twice dosed) plasma concentration vs time profiles from the integrated analysis are presented in Figure 23 and pharmacokinetic parameters are presented in Table 22.

Figure 23 demonstrates that ***neffy*** 2 mg was dose proportional and similar between once in each nostril (L/R) or twice in one nostril (R/R). The exposures from ***neffy*** 2 mg dosed twice were similar to 0.3 mg EpiPen dosed twice. In all ARS studies, IM injection regardless of device used did not result in dose proportional increases in exposures.

Figure 23: Plasma Concentration vs Time Profiles of Epinephrine, Twice Dosed, by Treatment



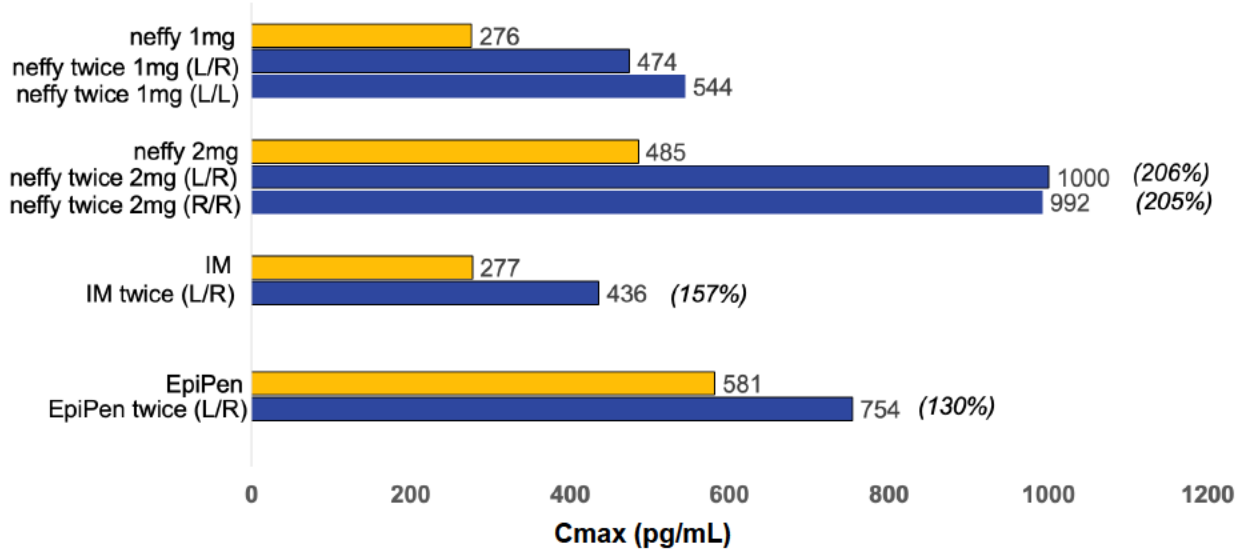
Statistical significance
neffy 2.0 mg (R/R) vs. Epinephrine 0.3 mg IM (L/R): 12.5 to 360 min ($p<.01$)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 4, 60 to 240 min ($p<.01$), 6, 8, 30, 45 and 360 min ($p<.05$)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 6 to 10, 30 to 240 min ($p<.01$), 4, 20, 30 min ($p<.05$)

Table 22: Summary Statistics of Total Epinephrine Pharmacokinetic Parameters: Twice-Dosed Treatments

Treatment	N	C_{max} (pg/mL)	$pAUC_{0-20}$ (min*pg/mL)	$pAUC_{0-45}$ (min*pg/mL)	AUC_{0-t} (min*pg/mL)	t_{max} (min)
		Mean(%CV)				median (range)
neffy **2 mg twice (L/R)**	**39**	**1000 (93)**	**5430 (99)**	**22000 (97)**	**86000 (77)**	**30 (6 -150)**
neffy **2 mg twice (R/R)**	**39**	**992 (75)**	**5610 (94)**	**22500 (82)**	**86500 (61)**	**30 (4 – 150)**
Epinephrine 0.3 mg IM twice (L/R)	70	436 (49)	2750 (83)	9610 (59)	47500 (33)	45 (6 – 180)
EpiPen 0.3 mg twice (L/R)	78	754 (65)	6930 (77)	18300 (54)	55000 (48)	20 (4 – 360)

Statistical significance
neffy 2.0 mg (L/R) vs. Epinephrine 0.3 mg IM (L/R): Cmax, $pAUC_{0-20}$, $pAUC_{0-45}$, AUC_{0-t} ($p<.01$)
neffy 2.0 mg (R/R) vs. Epinephrine 0.3 mg IM (L/R): Cmax, $pAUC_{0-20}$, $pAUC_{0-45}$, AUC_{0-t} ($p<.01$)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): AUC_{0-t} ($p<.01$)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): AUC_{0-t} ($p<.01$), C_{max} ($p<.05$)

Figure 24: Dose Proportionality Following Twice Dosed Treatments



5.2. Integrated Pharmacodynamic Results

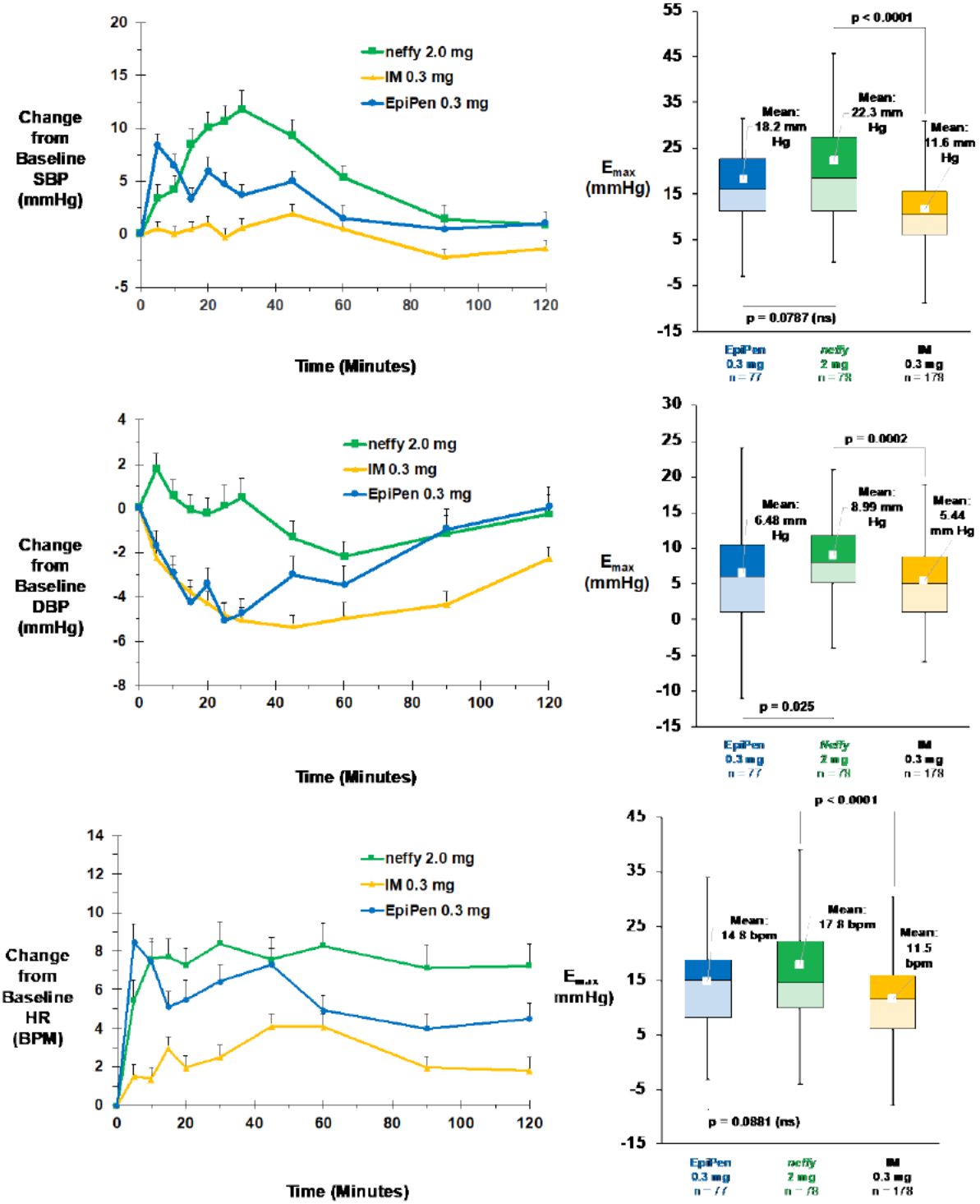
In general, *neffy* 2 mg dosed once resulted in pharmacodynamics responses that were comparable to or better than injection products (Figure 25 and Table 23). Changes and absolute values of blood pressure and heart rate were within normal physiologic levels as observed during daily activities such as exercise or climbing several flights of stairs. Change from baseline for systolic blood pressure and heart rate were similar (not significantly different) from EpiPen, but generally statistically greater than 0.3 mg IM injection. For diastolic blood pressure there was a greater drop after IM injection than with intranasal administration due to the direct to systemic route of administration (i.e., similar to intravenous infusion) (Tanimoto-2022).

With twice dosing of ***neffy*** 2 mg (Figure 26 and Table 24) pharmacodynamic responses were generally statistically greater for systolic blood pressure increase as compared to EpiPen and IM injection. This greater mean increase in systolic blood pressure is likely due to the fact that the pharmacokinetics of injection products are not dose proportional and the significant drop in diastolic blood pressure that suppresses the increase in systolic blood pressure. However, given that when a second dose is needed, the reaction is generally more severe and the patient is more likely hypotensive due to vasodilation from histamine and other mediators, ***neffy's*** greater increase in systolic blood pressure is generally considered beneficial. Changes in heart rate were similar to EpiPen (not significantly different) but greater than IM injection.

5.2.1. Pharmacodynamics of Once Dosed Treatments

Mean plots of change from baseline pharmacodynamic parameters versus time, are presented in Figure 25 and a summary of pharmacodynamic parameters are presented in Table 23. In general, ***neffy*** 2 mg IN resulted in pharmacodynamics responses that were comparable to or better than injection products.

Figure 25: Single Dose: Mean Change from Baseline PD vs Time and Box Plots



Statistical significance

SBP:	neffy 2.0 mg vs. Epinephrine 0.3 mg IM:	5 -90 min ($p<0.0001$ to <0.05)
	neffy 2.0 mg vs. EpiPen 0.3 mg:	5 min and 15-60 min ($p<0.01$ to <0.05)
DBP:	neffy 2.0 mg vs. Epinephrine 0.3 mg IM:	5 -120 min ($p<0.0001$ to <0.05)
	neffy 2.0 mg vs. EpiPen 0.3 mg:	5 – 30 min ($p<0.0001$ to <0.01)
HR:	neffy 2.0 mg vs. Epinephrine 0.3 mg IM:	5 -120 min ($p<0.0001$ to <0.01)
	neffy 2.0 mg vs. EpiPen 0.3 mg:	15, 60, and 90 min (<0.05)

Table 23: Integrated Pharmacodynamic Response, Once Dosed, by Treatment

Treatment	N	E_{max} mean (%CV)			T_{Emax} median (range)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
Epinephrine 0.3 mg IM	142	11.6 (74)	5.44 (125)	11.5 (70)	25 (1 - 120)	9 (1 - 120)	29.5 (1 - 120)
EpiPen 0.3 mg	77	18.2 (68)	6.48 (112)	14.8 (61)	16 (1 - 119)	21 (1 - 119)	17 (1 - 115)
***neffy* 2 mg**	**78**	**22.3 (72)**	**8.99 (73)**	**17.8 (69)**	**25 (1 - 120)**	**19 (1 - 120)**	**19.5 (1 - 120)**

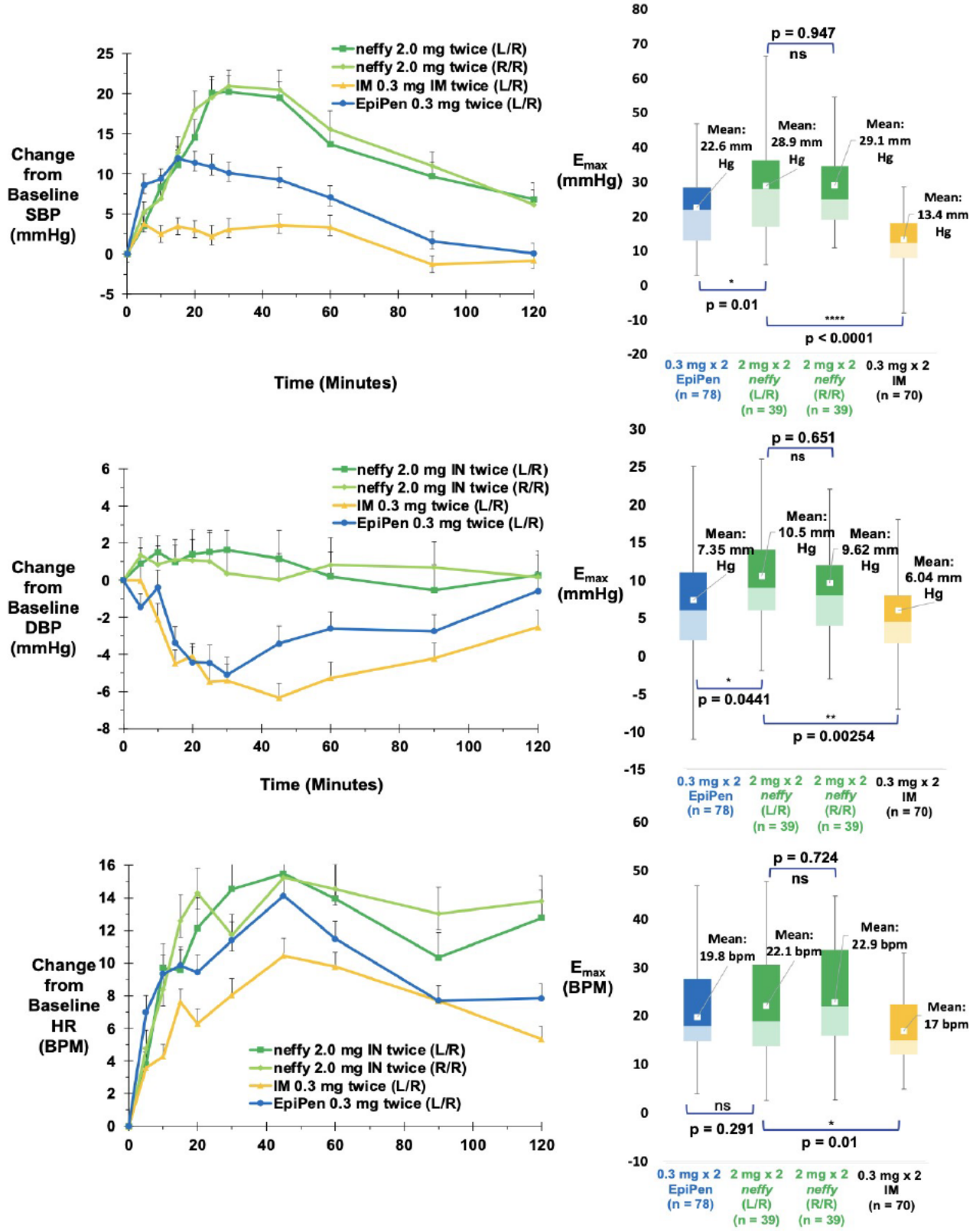
Statistical significance
neffy 2.0 mg vs. Epinephrine 0.3 mg IM: SBP E_{max} ($p<0.0001$), DBP E_{max} ($p<0.001$), HR E_{max} ($p<0.0001$)
neffy 2.0 mg vs. EpiPen 0.3 mg: DBP E_{max} ($p<0.05$)

5.2.2. Pharmacodynamics of Twice Dosed Treatments

Mean plots of change from baseline pharmacodynamic parameters versus time, are presented in Figure 26 and a summary of pharmacodynamic parameters are presented in Table 23.

Consistent with the once dosed treatments, ***neffy*** 2 mg IN resulted in pharmacodynamics responses that were comparable to or better than injection products.

Figure 26: Twice Dosing: Mean Change from Baseline PD Response vs Time and Box Plots



Statistical significance
SBP: neffy 2.0 mg (L/R) vs. Epinephrine 0.3 mg IM (L/R): 10 to 120 min ($p<0.0001$ to <0.01)
neffy 2.0 mg (R/R) vs. Epinephrine 0.3 mg IM (L/R): 10 to 120 min ($p<0.0001$ to <0.05)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 5 and 25 to 120 min ($p<0.0001$ to <0.05)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 20 to 120 min ($p<0.0001$ to <0.05)
DBP: neffy 2.0 mg (L/R) vs. Epinephrine 0.3 mg IM (L/R): 10 to 90 min ($p<0.0001$ to <0.05)
neffy 2.0 mg (R/R) vs. Epinephrine 0.3 mg IM (L/R): 10 to 90 min ($p<0.0001$ to <0.05)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 15 to 45 min ($p<0.0001$ to <0.01)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 5, 15 to 90 min ($p<0.001$ to <0.05)
HR: neffy 2.0 mg (L/R) vs. Epinephrine 0.3 mg IM (L/R): 5, 10, 20 to 60, 120 min ($p<0.0001$ to <0.05)
neffy 2.0 mg (R/R) vs. Epinephrine 0.3 mg IM (L/R): 5 to 120 min ($p<0.0001$ to <0.05)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 120 min ($p<0.01$)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): 90, 120 min ($p<0.01$)

Table 24: Integrated Pharmacodynamic Response, Twice Dosed, by Treatment

Treatment	N	E_{max} mean (%CV)			T_{Emax} median (range)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
***neffy* 2 mg twice (L/R)**	**39**	**28.9 (47)**	**10.5 (71)**	**22.1 (55)**	**29 (2 - 116)**	**19 (1 - 115)**	**29 (1 - 116)**
***neffy* 2 mg twice (R/R)**	**39**	**29.1 (46)**	**9.6 (84)**	**22.9 (44)**	**28 (6 - 85)**	**13 (1 - 118)**	**40 (1 - 116)**
Epinephrine 0.3 mg IM twice (L/R)	70	13.4 (71)	6.0 (116)	17 (45)	22 (1 - 120)	5 (1 - 120)	45 (2 - 120)
EpiPen 0.3 mg twice (L/R)	78	22.6 (52)	7.4 (109)	19.8 (50)	19 (1 - 88)	16 (1 - 119)	29 (1 - 119)

Statistical significance
neffy 2.0 mg (L/R) vs. Epinephrine 0.3 mg IM (L/R): SBP E_{max} ($p<0.0001$), DBP E_{max} ($p<0.01$), HR E_{max} ($p<0.05$)
neffy 2.0 mg (R/R) vs. Epinephrine 0.3 mg IM (L/R): SBP E_{max} ($p<0.0001$), DBP E_{max} ($p<0.05$), HR E_{max} ($p<0.001$)
neffy 2.0 mg (L/R) vs. EpiPen 0.3 mg (L/R): SBP E_{max} ($p<0.05$), DBP E_{max} ($p<0.05$)
neffy 2.0 mg (R/R) vs. EpiPen 0.3 mg (L/R): SBP E_{max} ($p<0.01$)

5.2.3. Differences in Pharmacodynamic Response by Route

The pharmacodynamic results were mostly comparable between ***neffy*** and EpiPen despite the higher and faster pharmacokinetic profile of EpiPen. The difference in the DBP response between ***neffy*** and injection products may be attributed to the route of administration (Tanimoto-2022). Activation of the β_2 adrenergic receptors promotes vasodilation in the skeletal muscle, causing a decrease in peripheral vascular resistance and increased blood flow to skeletal muscle, ultimately resulting in a decrease in DBP (Westfall-2011). However, such decrease in DBP may be more enhanced when epinephrine is administered into the skeletal muscle directly via injection (100% epinephrine) rather than from the systemic circulation. Intranasal epinephrine

will enter the systemic circulation after absorption from the nose followed by going through the venous and the heart, and the skeletal muscle may be exposed to only 15-20% of the total epinephrine dose based on the distribution of cardiac output at rest (Klabundel-2021). Such differences due to route of administration have been reported using a dog anaphylaxis model where IM injection of epinephrine decreased mean arterial pressure, pulmonary wedge pressure and cardiac output (Figure 27) (Mink-2004).

Figure 27: Pharmacodynamic Responses by Route of Administration in Dog Anaphylaxis

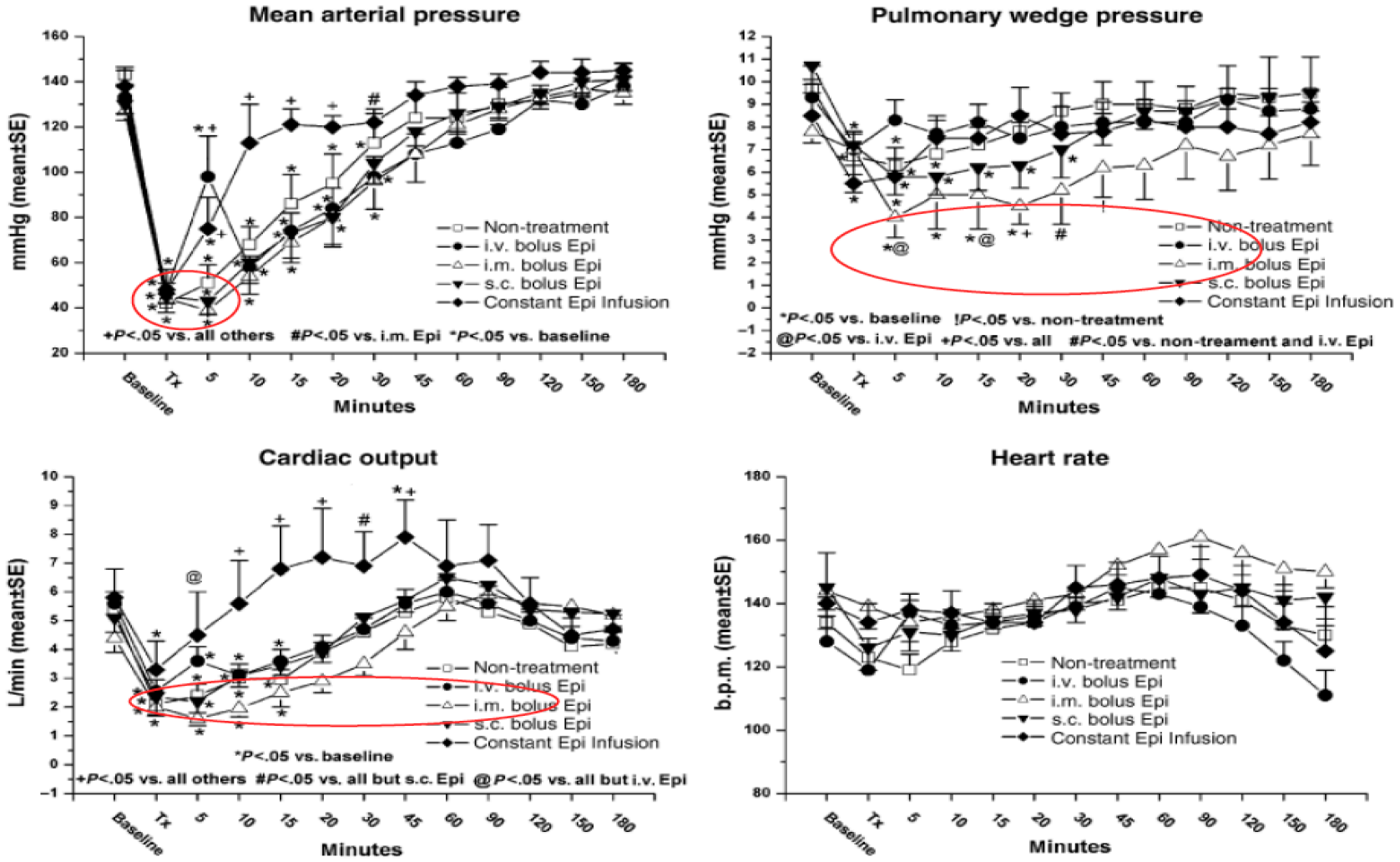


Fig. 1. Haemodynamic parameters are plotted over the course of the study (mean ± SE). Measurements were obtained at baseline, treatment (Tx), and until 3 h post-treatment. $N = 6$ for all parameters at all intervals. Epi, epinephrine; i.v., intravenous; i.m., intramuscular, and s.c., subcutaneous. Statistics by two-way ANOVA and Student–Newman–Keuls' multiple comparison test.

5.3. Pediatric Data from Type I Allergy Patients – EPI 10

Study EPI 10 (Interim Analysis) was conducted to assess the pharmacokinetics and pharmacodynamics of ***neffy*** in pediatric allergy patients. During the course of development of ***neffy***, ARS increased the dose from 1.0 to 2.0 mg. Accordingly, the pediatric dose was increased as shown in Table 25 below.

Table 25: History of Pediatric Dose

	Previous Dose	Current Dose
15 kg to <30 kg	0.65 mg	1.0 mg
≥30 kg	1.0 mg	2.0 mg

This study is currently ongoing; the data presented below are interim data. At the time of the interim analysis, the sample size for the ***neffy*** 1 mg, 15 kg to <30 kg group was only three subjects; therefore, the summary statistical results of that group are not presented.

The pediatric study results demonstrate that 1) the pharmacokinetics of ***neffy*** 2 mg in pediatric subjects is consistent with adults and dose proportional between 1 mg and 2 mg, and 2) that the change from baseline PD responses are comparable to what is observed in adults.

5.3.1. Pediatric Pharmacokinetics Results

The pharmacokinetic results of the interim analysis (Table 26) demonstrate that in children ≥30 kg, ***neffy*** 2 mg results in epinephrine absorption that is comparable-to-slightly higher than what is observed in adults and expected based on the Pharmacologically Based Absorption Model (PBAM). Epinephrine levels between the 1 and 2 mg doses in children ≥30 mg appear to be dose proportional.

Table 26: Summary Statistics of Epinephrine Pediatric Pharmacokinetic Parameters by Treatment

Product	N	Mean C_{max} (pg/mL) (CV%)	Median T_{max} (minutes) (range)	$pAUC_{0-20}$ (min*pg/mL) Mean (CV%)	$pAUC_{0-45}$ (min*pg/mL) Mean (CV%)	AUC_{0-t} (min*pg/mL) Mean
neffy 1.0 mg Children ≥ 30 kg (previous dose)	25	253 (66)	20 (8-120)	2570 (78)	5960 (52)	14000 (53)
neffy 2.0 mg Children ≥ 30 kg	16	540 (71)	25 (3-120)	4140 (78)	13500 (76)	35500 (76)
neffy 2.0 mg Adults (Integrated)	78	485 (71)	21 (2-150)	3610 (84)	11000 (76)	40900 (68)

Larger children (30+ kg) have similar but slightly higher exposures as compared to adults with 2 mg
Proportional results between 1 mg and 2 mg doses in 30+ kg group
Data supported by Pharmacologically Base Absorption Model (PBAM) and POP PK

5.3.2. Pediatric Pharmacodynamic Results

Change from baseline PD responses are presented in Table 27. ***neffy*** elicited SBP and HR responses comparable to what is observed in adults.

Table 27: Pediatric Pharmacodynamic Parameters for PD Change from Baseline

Treatment	N	E_{max} mean (%CV)			T_{Emax} median (range)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
neffy 1.0 mg Children ≥ 30 kg (previous dose)	25	8.23 (85)	4.92 (91)	13.8 (72)	20 (0 – 120)	15.5 (0 – 122)	18 (0 – 124)
neffy 2.0 mg Children ≥ 30 kg	16	11.9 (69)	7 (76)	15.4 (75)	25 (0 – 90)	17.5 (0 – 120)	32.5 (0 – 90)
neffy 2.0 mg Adults (Integrated)	78	22.3 (72)	8.99 (73)	17.8 (69.3)	25 (1 - 120)	19 (1 - 120)	19.5 (1 - 120)

5.4. Various Dosing Conditions

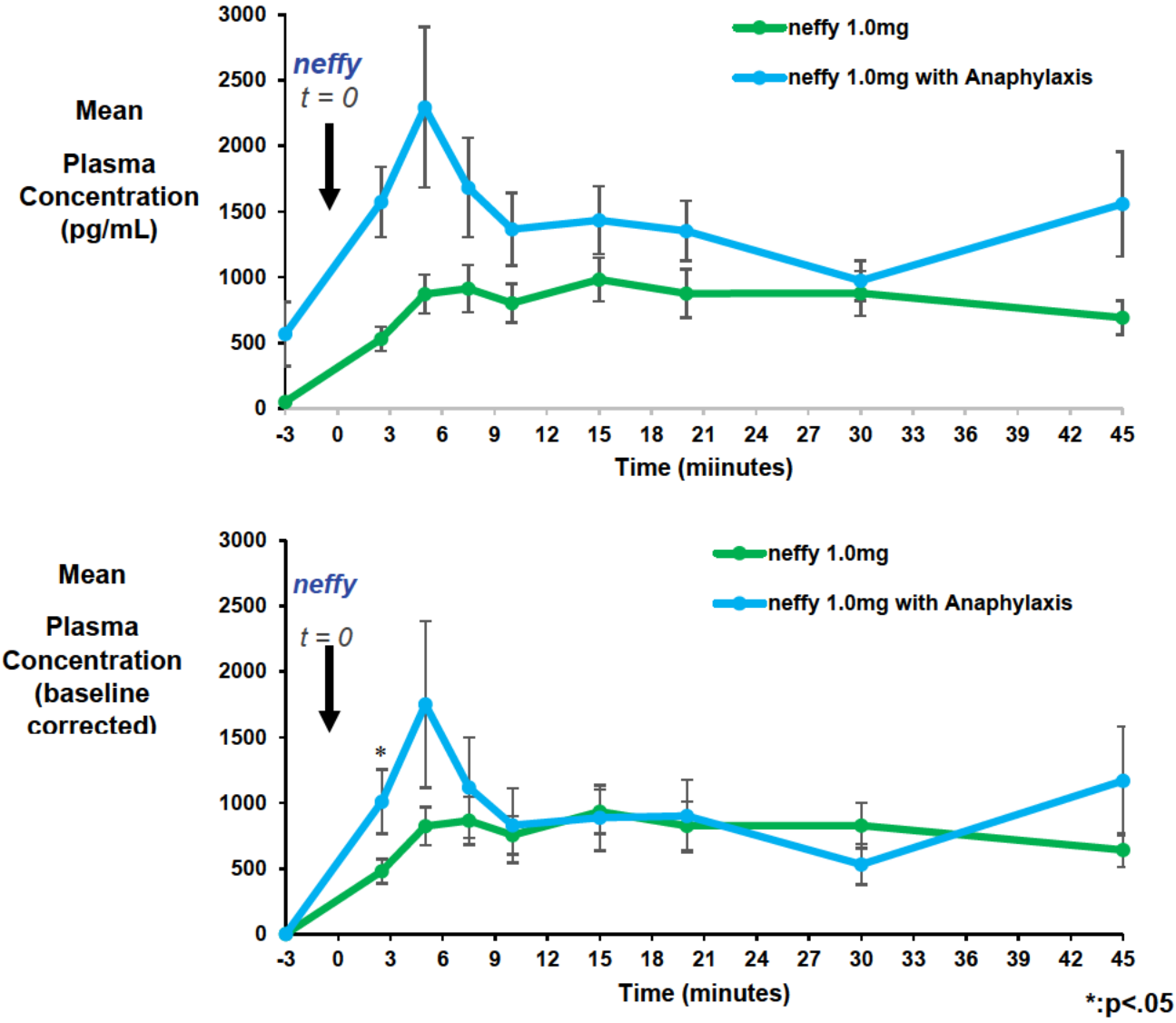
Since both ethical and practical limitations preclude the conduct of clinical trials in patients experiencing severe allergic reactions and anaphylaxis, ARS also conducted a GLP study using a dog anaphylaxis model to assess absorption during acute anaphylaxis. Furthermore, ARS conducted two clinical trials to assess the pharmacokinetics and pharmacodynamics of ***neffy*** in subjects with allergic rhinitis (EPI 16) and upper respiratory tract infections (EPI 14) in order to evaluate the effect of nasal edema and congestion on the absorption of epinephrine administered via ***neffy***.

5.4.1. Effect of Hypotension during Anaphylaxis (GLP Dog Anaphylaxis Model)

A GLP study using a dog anaphylaxis model was conducted to evaluate the pharmacokinetics of ***neffy*** in anesthetized beagle dogs under both normal conditions and Tween 80-induced anaphylaxis conditions. A total of 14 dogs (10 males and 4 females) were dosed with ***neffy*** 1 mg under normal conditions, followed by ***neffy*** 1 mg under anaphylaxis conditions. All dogs showed signs of allergic reaction/anaphylaxis following administration of Tween 80.

During anaphylaxis, blood pressure decreased from 137±50.4/78±30 mmHg to 61±10/39±7 mmHg. ***neffy*** was absorbed rapidly and extensively by the IN route with C_{max} at least as great and T_{max} at least as rapid as when in a normal state. Thus, absorption during an anaphylactic reaction was confirmed to be at least as good as when the dogs were in a normal state.

Figure 28: Absorption During Hypotension: GLP Dog Anaphylaxis Model



5.4.2. Effect of Allergic Rhinitis (EPI 16)

EPI 16 was conducted to evaluate the comparative bioavailability of ***neffy*** 2 mg with and without induced allergic rhinitis by nasal allergen challenge (NAC) relative to Epinephrine 0.3 mg IM. EPI 16 was conducted under worst case dosing conditions with ***neffy*** administered immediately after NAC induction when symptoms of congestion and rhinorrhea were greatest.

EPI 16 utilized the Total Nasal Symptom Score (TNSS) questionnaire to evaluate the nasal symptoms per FDA's guideline (Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry). ***neffy*** 2 mg was administered immediately after rhinitis was induced when symptoms such as congestion and rhinorrhea were most significant.

The criteria for subjects to be dosed with ***neffy*** 2 mg in the EPI 16 clinical study was that they had to have a TNSS of ≥5 out of 12 and a congestion score of ≥2 out of 3 for at least one allergen during the screening challenge. There were 30 of the 34 subjects who reported positive symptoms of rhinorrhea (runny nose) based on the TNSS scoring after NAC induction and before dosing of ***neffy*** 2 mg.

Pharmacokinetic Results

Relative to normal nasal conditions, allergic rhinitis resulted in a more rapid (T_{max}) absorption of epinephrine (Figure 9 and Table 9), presumably due to increased permeability which was observed in the anaphylaxis dog model (Section 1.6.4.1) and also is reported in the literature (Tuttle-2020). The T_{max} with ***neffy*** 2 mg with rhinitis was 7 minutes as compared to 20 minutes in the normal nasal state. T_{max} with ***neffy*** 2 mg with rhinitis was also significantly more rapid than IM epinephrine injection (7 min vs. 45 min, $p<0.0001$).

At the same time, ***neffy*** 2 mg with rhinitis resulted in more rapid clearance (i.e., lower C_{max} and overall AUC_{0-t}) compared to normal nasal conditions, which may be due to rhinitis symptoms such as associated rhinorrhea (i.e., more rapid nasal fluid flow resulting in increased clearance of drug from the nasal mucosa). Rhinorrhea was observed in most of the subjects (30 of 34 subjects in the rhinitis group). While the C_{max} was lower with rhinitis as compared to that with ***neffy*** 2 mg in the normal nasal state, the maximum exposure (C_{max}) with rhinitis was still compable to IM Epinephrine 0.3 mg (Cmax 303 vs 259 pg/mL, $p>0.05$).

Figure 29: Plasma Concentration vs Time Profiles of Epinephrine (EPI 16)

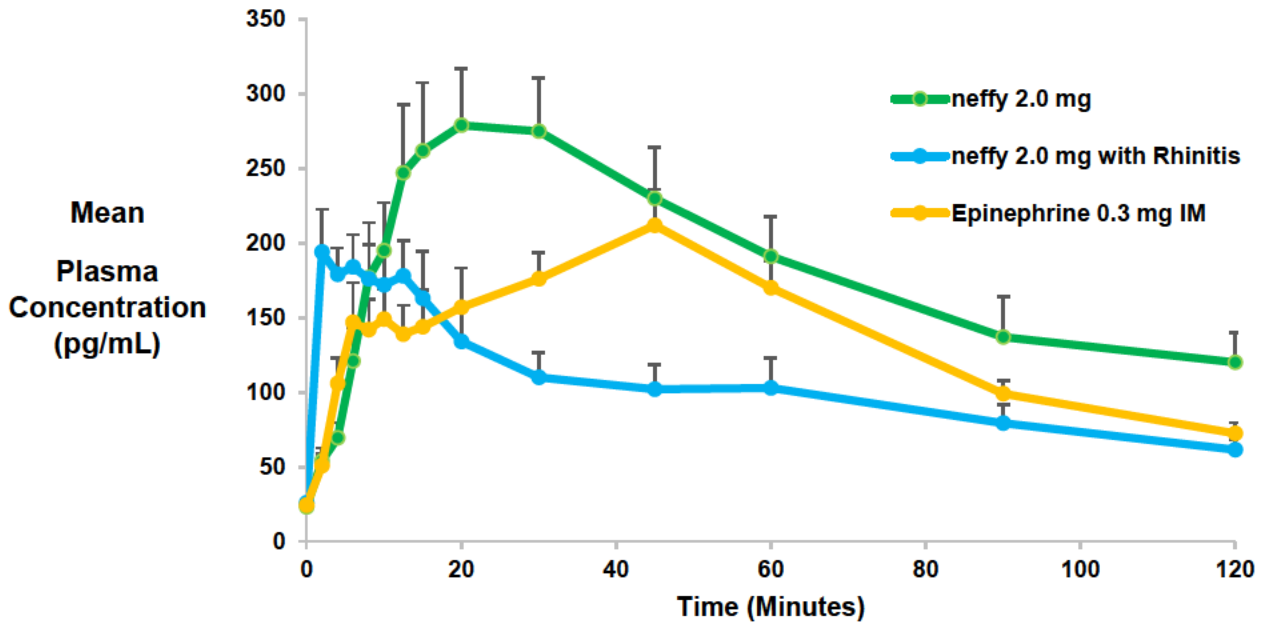


Table 28: Pharmacokinetic Parameters, by Treatment (EPI 16)

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL) mean (%CV)	AUC_{last} (min*pg/mL) mean (%CV)
***neffy* 2.0 mg**	36	20 (2 – 120)	491 (65.2)	37100 (66.1)
***neffy* 2.0 mg with rhinitis**	34	7 (2 – 90)*	303 (67.7)	23300 (69.0)
Epinephrine 0.3 mg IM	35	45 (4 – 360)	259 (61.7)	26000 (41.9)

*neffy 2.0 mg with rhinitis vs. Epinephrine 0.3 mg IM: tmax ($p<0.0001$)

As seen in Table 29 below, ***neffy*** 2 mg with rhinitis results in epinephrine exposures that are significantly greater than IM injection from 2 minutes after administration (first time point) and through the first 30 minutes followed by comparable exposures.

Table 29: Partial AUC Results (EPI 16)

Treatment	N	pAUC (min*pg/mL)						
		AUC_{0-2min}	AUC_{0-4min}	AUC_{0-6min}	AUC_{0-8min}	$AUC_{0-10min}$	$AUC_{0-12.5min}$	$AUC_{0-15min}$
		mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)
ARS-1 2.0 mg	36	77.1 (83.4)	201 (81.0)	391 (81.9)	688 (90.5)	1060 (92.8)	1630 (85.6)	2270 (83.5)
ARS-1 2.0 mg with rhinitis	34	212* (78.9)	569* (69.1)	922* (60.1)	1270* (58.0)	1610* (57.8)	2050* (56.4)	2460* (58.7)
Epinephrine IM 0.3 mg	35	68.5 (69.6)	211 (69.7)	439 (78.7)	700 (82.7)	966 (79.8)	1290 (77.4)	1610 (77.7)
Treatment	**N**	**pAUC (min*pg/mL)**						
		$AUC_{0-20min}$	$AUC_{0-30min}$	$AUC_{0-45min}$	$AUC_{0-60min}$	$AUC_{0-120min}$	AUC_{0-6h}	AUC_{1-6h}
		mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)	mean (%CV)
ARS-1 2.0 mg	36	3630 (78.7)	6400 (67.1)	10200 (62.4)	13400 (62.1)	22200 (65.7)	38700 (62.2)	25000 (76.8)
ARS-1 2.0 mg with rhinitis	34	3200* (65.9)	4400* (70.9)	5970 (72.9)	7500 (76.4)	12400 (77.7)	24000 (66.0)	16500 (64.8)
Epinephrine IM 0.3 mg	35	2280 (79.5)	3790 (76.5)	6430 (69.8)	9030 (66.3)	15200 (54.5)	27000 (39.1)	17800 (38.0)

* neffy 2.0 mg with rhinitis vs. Epinephrine 0.3 mg IM: pAUC 2 to 20 min ($p<0.01$), 30 min ($p<0.05$)

If evaluating PK results based on absolute concentrations (Table 30), the concentration of epinephrine after administration of ***neffy*** 2 mg with rhinitis is greater after the first time point at 2 and 4 minutes and comparable to the IM until after 20 minutes.

Table 30: Summary Statistics of Epinephrine C_{max} By Time Point Results (EPI 16)

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL) Mean (%CV)	Epinephrine Concentration at Each Time Point mean (%CV)					
				2 min	4 min	6 min	10 min	15 min	20 min
ARS-1 2.0 mg	36	20.0 (2-120)	491 (65.2)	54 (95)	70 (88)	121 (113)	195 (97)	262 (103)	279 (82)
ARS-1 2.0 mg with rhinitis	34	7.00 (2-90)	303 (67.7)	194* (85)	179* (56)	184 (68)	172 (74)	163 (109)	133 (100)
Epinephrine IM 0.3 mg	35	45.0 (4-360)	259 (61.7)	51 (84)	106 (86)	147 (99)	149 (75)	144 (95)	157 (93)

* neffy 2.0 mg with rhinitis vs. Epinephrine 0.3 mg IM: 2 to 4 min ($p<0.01$)

Clinical effect with epinephrine is observed within 5 to 10 minutes after administration of IM injection with approximately 90% of all events resolving with a single dose and only approximately 10% requiring a second administration to resolve symptoms (Patel-2021). The need for a second dose is also related to severity of the event and if epinephrine administration was delayed (Hochstadter-2016, Patel-2021), and thus with prompt administration after symptoms are detected the need for a second dose may be further reduced. Prescribing guidelines (Shaker-2020) are clear that administration of a second dose of epinephrine should occur if response is not observed in 5 to 10 minutes.

Thus, ***neffy*** 2 mg even with NAC induced rhinitis will give greater exposures of epinephrine than IM injection through the first 20 to 45 minutes based on absolute concentration or overall exposure respectively. If a second dose is administered with either ***neffy*** 2 mg or IM injection with epinephrine the additional administration would occur before IM injection reaches peak concentration (t_{max} = 45 minutes) and in the time frame where ***neffy*** 2 mg has overall higher exposures compared to IM through at least 20 minutes. Therefore, even if more rapid clearance of the drug from the nasal mucosa may occur during allergic rhinitis, it is not anticipated to result in any clinically meaningful difference in effectiveness relative to IM injection of epinephrine. If effect is not observed in the first 5 to 10 minutes, a second dose would be given. The second dose would likely have absorption more similar to dosing with normal nasal conditions given the known effect of epinephrine to reverse nasal congestion and rhinorrhea (Macmillan-2022).

Pharmacodynamic Results

The overall pharmacodynamic effect of ***neffy*** 2 mg with rhinitis was similar to both doses of IM Epinephrine (Figure 30 and Table 12).

Figure 30: EPI 15 PD Results: Box Plots

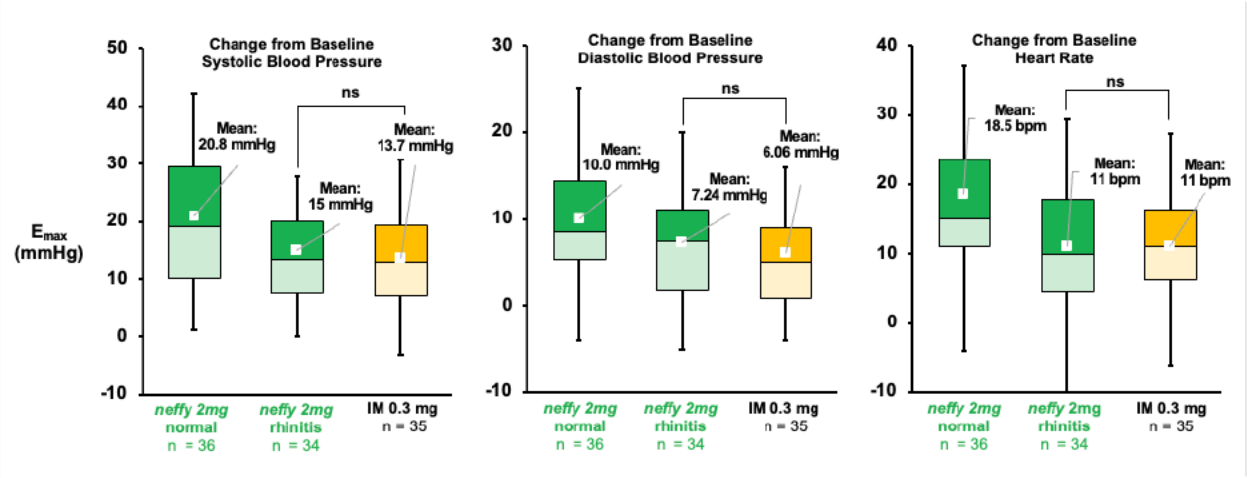


Table 31: Pharmacodynamic Parameters, by Nasal Condition

Treatment	N	E_{max} mean (%CV)			T_{Emax} median (range)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
***neffy* 2 mg**	36	20.8 (80.6)	10.0 (77.2)	18.5 (75.9)	26.0 (1.00-120)	25.0 (1.00-120)	25.0 (1.00-178)
***neffy* 2 mg with rhinitis**	34	15.0 (83.4)	7.24 (6.56)	11.0 (111)	19.0 (1.00-120)	27.5 (1.00-119)	9.00 (1.00-119)
Epinephrine IM 0.3 mg	35	13.7 (71.1)	6.06 (128)	11.0 (70.6)	19.0 (1.00-123)	15.0 (1.00-123)	44.0 (2.00-120)

5.4.3. EPI 14 – Upper Respiratory Tract Infection

EPI 14 was conducted to evaluate the comparative bioavailability of ***neffy*** 2 mg with and without nasal edema and congestion resulting from an upper respiratory tract infection (URTI). The results from the preliminary data are summarized in Figure 31 and Table 32 based on plasma-concentration vs. time curves and mean change in systolic blood pressure over time and PK parameters. These results support that there was an insignificant impact on the pharmacokinetic or pharmacodynamic results from ***neffy*** 2 mg with natural infectious rhinitis conditions caused by a cold, flu, sinus infection or other viral infections. This study further supports that the EPI 16 study where subjects were administered ***neffy*** 2 mg immediately after NAC induction of rhinitis may be worst case conditions and with normal rhinitis conditions that less impact on absorption would be observed.

Figure 31: Plasma Concentration and Systolic Blood Pressure Change vs. time (EPI 14)

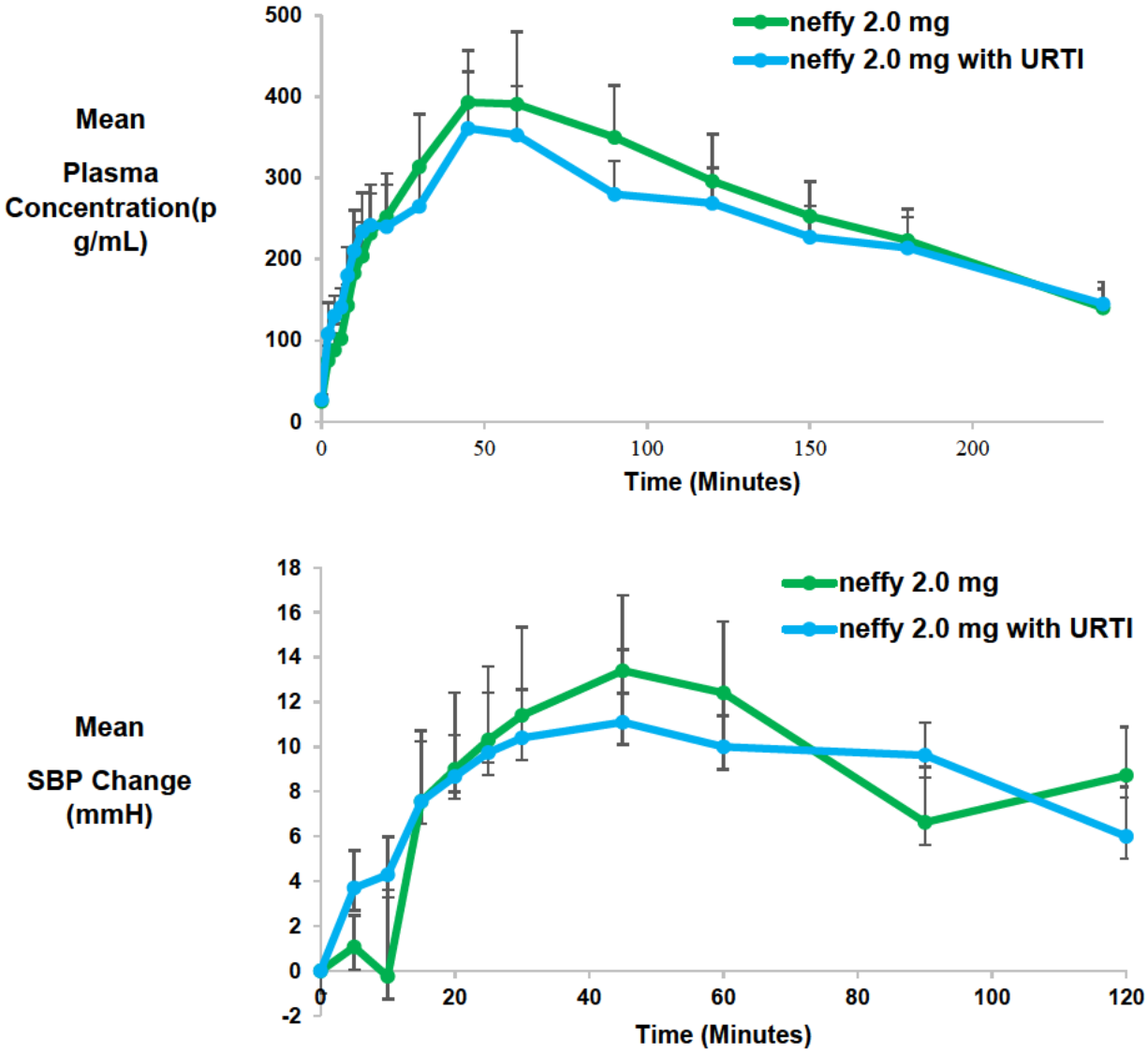


Table 32: Summary Statistics of Epinephrine Pharmacokinetic Parameters

Nasal Condition	N	C_{max} (pg/mL) Mean (%CV)	t_{max} (min) Median (range)	AUC_{0-t} (min*pg/mL) Mean (%CV)
ARS-1 2.0 mg with URTI	21	490 (67.2)	45.0 (1.60 – 150)	58700 (60.9)
ARS-1 2.0 mg normal nasal conditions	16	570 (56.1)	45.7 (9.90 – 150)	64400 (53.4)

5.5. Additional Analyses Across Studies

5.5.1. Population PK Modeling (POP PK)

A Population Pharmacokinetic (PPK) and Population Pharmacokinetic/Pharmacodynamics (PPK/PD) Modeling and Simulation were conducted to develop a population PK model to characterize the absorption and disposition of epinephrine in adults after intranasal administration via ***neffy*** and intramuscular administration via injection including needle/syringe and EpiPen. Leveraging the pharmacokinetic data from ***neffy*** studies in adults, the PK and PD outcomes for ***neffy*** were estimated for pediatric subjects with these simulated outcomes based on age groups: 4- <6 y, 6-<12 and 12-18 years.

Pediatric simulations suggest that AUC and C_{max} values overlap with adult AUC and C_{max} values with increasing exposure at lower weights. Changes in SBP and HR values in the pediatric groups overlap with adult values and thus support that the anticipated response based on these surrogate endpoints should be no different in children than adults.

5.5.2. Physiologically Based Absorption Model Analysis

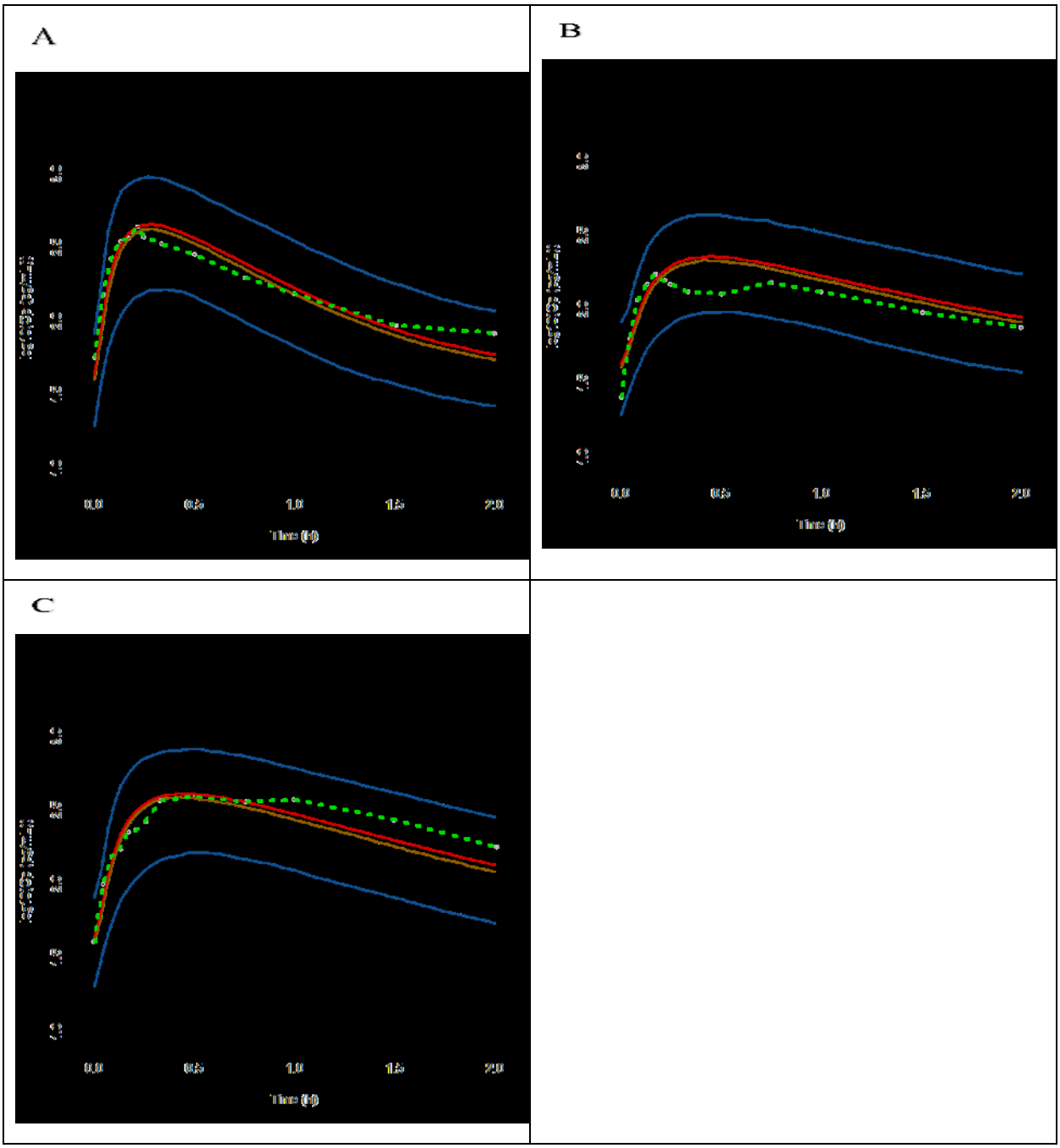
The model first developed in adults appropriately predicted the mean PK behavior as well as the variability. The simulated profiles were comparable to the clinical data and the predicted AUC_{last} and C_{max} values were within 1.5-fold of the observed value for all three clinical trials. Considering all of the above, the model was considered appropriate to predict epinephrine mean and population plasma concentrations after the IN administration of neffy in healthy adults.

The parameters of the population PBAM model for neffy were scaled to pediatrics to bridge the information to this population. Modeling was based on the adult population PK data in healthy subjects and then the inclusion of different scaling factors to extend epinephrine PK into pediatrics from 4 to 17 years of age.

All model development and verification simulations were done using virtual subjects matching as close as possible to those in clinical trials EPI 10 following the clinical study designs. Verification simulations were performed using a population of N=1500 subjects to assess the PK variability and simulated C_{max}, T_{max} and AUC were calculated and compared to the mean observed data.

A comparison of the simulated and observed plasma concentrations of epinephrine after the single IN dosing of neffy in study EPI 10 is shown in Figure 32. Mean observed concentrations of patients in EPI 10 and the predictions using the PBAM model in a virtual population (n =1500) are displayed in Figure 32.

Figure 32: Comparison of Epinephrine Plasma Profiles in Pediatrics from EPI 10



Comparison of epinephrine plasma profiles in pediatrics from study EPI 10 with the PBAM model predictions (the dashed green line is the mean profile from the observation; solid yellow, red and blue lines are the predicted median, mean and 95% PI using the PBAM model). A) 0.65 mg neffy 15-30kg, B) 1 mg neffy >30 kg, C) 2 mg neffy >30 kg

The model appropriately predicted the mean PK behavior in pediatric subjects. Predicted and observed plasma AUC_{last} and C_{max} mean values and T_{max} median values as well as the predicted over observed ratios for AUC_{last} and C_{max} are shown in Table 33.

Table 33: Simulated and Observed T_{max}, C_{max} and AUC_{0-t} values and Ratios for *neffy* Following a Single Dose in Children from EPI 10

	Median T_{max} (min)	Mean C_{max} (pg/ml)	ratio	Mean AUC_{last} (pg min/ml)	ratio
PBAM_1 mg_>30kg	26	226	-	18443	-
EPI_10_1 mg_>30kg*	20	253	0.89	14000	1.32
PBAM_2 mg_>30kg	26	408	-	31809	-
EPI_10_2 mg_>30kg*	25	540	0.76	35500	0.90

*Mean C_{max} and AUC_{last} calculate from non-compartment analysis of individual plasma profiles

Goodness-of-fit plots of predicted versus observed AUC_{last} values and of predicted versus observed C_{max} was assessed. In general, AUC_{last} and Cmax values are within the 1.5-fold range demonstrating the descriptive and predictive performance of ***neffy*** PBAM model both in adults and pediatrics. Considering all of the above, the model was considered appropriate to predict epinephrine plasma concentrations after the IN administration of ***neffy*** in adult and pediatric subjects.

For children weighing 15-30 kg a model refinement was needed to capture the mean observations from study EPI 10. For children 15 to <30 kg body weight, a 1 mg dose administered in the nose. For children 30 kg body weight or greater, a 2 mg dose administered in the nose. In order to ensure the safety and efficacy of the selected dose for the pediatric clinical trial the simulated plasma profiles were compared to that in adult healthy subjects after the 2 mg dose.

The predicted exposures, including the 95% confidence intervals are within the expected values from the 2 mg in >30 kg children and 1 mg in 15-30 kg administration of ***neffy*** in adults. The 2 mg IN dose produces plasma exposures in pediatrics (>30 kg) comparable to that in adults and slightly higher 97.5 percentile in 6-year-old children weighting 30 kg. Similarly, the 1 mg IN dose produces plasma exposures in pediatrics (15-30 kg) comparable to that in adults and slightly higher 97.5 percentile. However, the predicted exposure values in these pediatric scenarios (2mg_6yrs_30 kg; EPI10_1mg_15-30kg) were still within the observed exposures reported in the literature for epinephrine administered in different formulations (Moss-2021). Based on this, the predicted exposures are considered appropriate in any case with no safety concerns in any of the predicted groups.

5.5.2.1. Conclusions

In conclusion, this analysis indicates that the predicted exposures in pediatrics are in line with the expected values in adults supporting the 1 mg dose in children 15 to <30 kg and the 2 mg dose for children ≥30 kg and the general adolescents and adult populations.

5.5.3. Effect of Weight on Epinephrine Concentration

An exploratory analysis to determine the effect of body weight on C_{max} and AUC_{0-t} was performed as part of the Integrated Pharmacokinetic-Pharmacodynamic Analysis.

Increased body weight was associated with decreased systemic drug exposure (negative regression slope) following treatment with Epinephrine 0.3 mg IM, Epinephrine 0.3 mg IM twice, or EpiPen 0.3 mg twice. In contrast, ***neffy*** IN dosed once or twice was not shown to be statistically significantly affected by body weight, with P values >0.05 (Table 34).

Unlike bodyweight, there was no consistent relationship between BMI and drug exposure (a mix of negative and positive regression slope amongst the various formulations was observed) (Data not shown but presented in the Integrated Analysis Table 279 and Figures from 289 to 312).

Table 34: Linear Regression of Ln(C_{max}) and Ln($AUC_{0-240min}$) vs Body Weight (kg) for Total and Baseline Corrected Epinephrine, Sorted by Treatment

Treatment	Co-variate: Body Weight							
	Dependent Variable							
	Ln(C_{max})				Ln($AUC_{0-240min}$)			
	Epinephrine				Epinephrine			
	Baseline Corrected		Total		Baseline Corrected		Total	
	P value	Slope	P value	Slope	P value	Slope	P value	Slope
neffy 2 mg IN	0.187	-0.01194	0.200	-0.01052	0.918	0.0009762	0.977	0.0002129
neffy 2 mg IN twice (L/R)	0.498	-0.009521	0.512	-0.008777	0.687	-0.005257	0.751	-0.003722
neffy 2 mg IN twice (R/R)	0.585	-0.006426	0.566	-0.006591	0.204	-0.01424	0.187	-0.01352
Epinephrine 0.3 mg IM	0.022	-0.009371	0.014	-0.009016	0.098	-0.005750	0.039	-0.005274
Epinephrine 0.3 mg IM twice (L/R)	0.037	-0.01237	0.041	-0.01145	0.030	-0.009724	0.036	-0.008087
EpiPen 0.3 mg	0.942	0.0005607	0.989	0.0001057	0.129	-0.008272	0.071	-0.007702
EpiPen 0.3 mg twice (L/R)	0.025	-0.01358	0.021	-0.01329	0.268	-0.005487	0.249	-0.004955

5.6. Human Factors

ARS has completed an informative study and two human factor validation studies (a Primary and a Post-Validation Supplemental (Bridging) study) to demonstrate that ***neffy*** is easily used, and labeling is well understood by patients, caregivers, and passerby persons. The primary Human Factor Validation study was conducted based on the original labeling used in the EPI 12 self-administration clinical trial. The primary Human Factor Validation study included 90 subjects, consisting of 30 severe allergy patients, 30 caregivers, 15 passer-byes (people with no understanding of the disease or epinephrine), 15 medical professionals, and 15 children aged 12 to 17 who were also severe allergy patients. For adult participants there was no training, and they were able to use ***neffy*** without any notable errors simply by reading the blister package labeling (which would be carried with them) alone during both self-dosing or dosing a simulated patient. Children (severe allergy patients, age 12 to 17 years) were trained in advance of the study and then brought back to dose without further instruction with only the blister package labeling for reference. All children assessed (N=15) were able to use ***neffy*** correctly in a simulated emergency allergy situation based on prior training and the information on the blister backing (quick reference guide).

After modifications to the Instructions for Use (IFU) and Quick Reference Guide (QRG) to specify to insert the nozzle of the sprayer into the nose until the fingers touch the nose, and to hold straight, as well as improvements to the pictures demonstrating correct and incorrect dosing (based on observations in clinical studies), a Bridging Human Factor Validation Study was conducted in 60 persons with severe allergies to ensure that the labeling improvements did not result in any unanticipated negative outcomes. This bridging study included 60 persons: 15 untrained adult patients who self-administered, 15 untrained adults who were caregivers, 15 adolescents who self-administered without training, and 15 adolescents who self-administered with training. The outcome of this Bridging Human Factor Validation study was that all adults dosed without error and correctly per the IFU and QRG with a high degree of understanding based on the labeling. In trained adolescents, there were no significant errors and good understanding of the labeling. In untrained adolescents there was potential for some subjects to be surprised by the device activation, which in a few cases, caused the sprayer to come out of the nose after activation. Overall, the study demonstrated that all untrained adults can properly dose ***neffy*** without training and based on the IFU and QRG. Adolescents who were trained also had no errors, while adolescents who were first time users with no previous experience using the device may experience possible dosing errors by pulling the nozzle out of the nose right after activation. It could not be determined from this study if the behavior would result in any inadequate dosing.

Based on the two Human Factor Validation studies conducted, ***neffy*** can be easily used by patients, caregivers, adolescents, and passerby persons based on the IFU and QRG. For some adolescents training may be appropriate to gain experience with the device, and ARS is planning to ensure medical professionals train adolescents who may self-administer prior to prescribing

neffy. The updated IFU and QRG were well understood by subjects and did not result in any unanticipated dosing errors.

6. OVERVIEW OF EFFICACY

6.1. Overall Pharmacokinetic Assessment

The results of the pharmacokinetic data demonstrated that pharmacokinetics of ***neffy*** 2 mg once dosing including HCP- and self-administration were well within the range (bracketed by) of injection products as defined by 0.3 mg IM injection with needle and syringe and 0.3 mg EpiPen (Table 21).

neffy 2 mg dosed once and twice (L/R and R/R) were similar in exposure and comparable to EpiPen when dosed twice (R/L). Given there was no statistical difference between ***neffy*** 2 mg dosed once in each nostril (R/L) or twice in one nostril (R/R), there is no need to instruct users to alternate nostrils which can be a confusing instruction and lead to dosing errors (Table 27).

In studies with twice dosing, ***neffy*** 2 mg was dose proportional and similar if dosed once in each nostril (L/R) or twice in one nostril (R/R). The exposures from ***neffy*** 2 mg dosed twice were similar to 0.3 mg EpiPen dosed twice. In all ARS studies, IM injection regardless of device used did not result in proportional increases in exposures (Table 27). If a second dose is needed, the reaction is more serious and ***neffy*** provides dose proportional second dose, unlike injection products where the second dose is less than dose proportional.

6.2. Overall Pharmacodynamics Assessment

Pharmacodynamic data indicate that ***neffy*** 2 mg results in pharmacodynamic responses (SBP and HR) that are comparable to EpiPen, and comparable to or better than IM injection with needle and syringe, likely resulting in more consistent activation of α- and β-adrenergic receptors. The comparable PD response of ***neffy*** relative to EpiPen despite differences in pharmacokinetic results may be due to the route of administration dependent differences in β2-mediated vasodilation in the thigh. Considering that there may be some degree of mast cell mediator-induced vasodilation occurring during allergic reaction, the ***neffy*** administration avoiding injection into the thigh should not undermine epinephrine's efficacy.

6.3. Various Case Dosing Assessment

ARS also conducted a GLP study using a dog anaphylaxis model to assess absorption during acute anaphylaxis, clinical studies in subjects with allergic rhinitis (EPI 16) in subjects with upper respiratory tract infections (EPI 14) in order to evaluate the effect of nasal edema and congestion on the absorption of epinephrine administered via ***neffy***.

- Dog Anaphylaxis model supports that epinephrine absorption following ***neffy*** does not appear to be negatively impacted by the hypotension caused by anaphylaxis; and in fact may be enhanced by an increase in vascular permeability.

- NAC induction of rhinitis resulted in more rapid absorption (edema) but more rapid clearance (rhinorrhea). Overall Cmax and tmax were superior to IM injection (needle and syringe). pAUC was greater for ***neffy*** through 30 to 45 min and absolute concentration was greater through 15 to 20 minutes. Since a second dose is administered 5 to 15 minutes following the initial dose if no effect observed in the first 5 to 10 minutes, this change in PK is not considered to be clinically meaningful and a second dose of ***neffy*** would be administered within the time frame where exposure was greater for ***neffy*** then injection.

- Infectious Rhinitis (URTI) resulted in less change between normal and rhinitis conditions, compared to NAC induction of rhinitis, where *neffy* was administered immediately after when symptoms of rhinitis and congestion were greatest.

Overall, epinephrine is absorbed at least as well during hypotension caused by anaphylaxis with absorption perhaps being enhanced by an increase in vascular permeability. This increase in absorption was also observed in the study with allergic rhinitis. However, accompanying symptoms such as rhinorrhea may reduce overall exposure. There was no meaningful impact on pharmacokinetics while dosing ***neffy*** in patients with URTI. There is a low risk from Rhinitis anticipated and there is only negative impact on pharmacokinetics when rhinorrhea is present. However, ***neffy*** concentrations in all scenarios are greater than IM injection for at least the first 15 to 20 minutes, during which a second dose is administered if no observed effect in 5-15 minutes (current treatment guidelines and labeling).

7. OVERVIEW OF SAFETY

7.1. Relevant Animal Toxicity and Product Quality Information

The toxicology of epinephrine is well understood in the literature and epinephrine is an approved product in many countries. The ***neffy*** formulated with 0.25% DDM has been evaluated after intranasal administration in rats at concentrations up to 0.8 mg. At doses higher than the human therapeutic doses, a 2-year carcinogenicity study with epinephrine injection, showed no carcinogenic effects in male or female F344/N rats exposed to aerosols containing 1.5 or 5 mg/m^3 l- epinephrine for 2 years or in B6C3F1 mice exposed to 1.5 or 3 mg/m^3 l-epinephrine for 2 years (Dietz-1990).

Single intranasal instillation of ***neffy*** in a rat at a dose up to 0.8 mg was not associated with any adverse findings. Some microscopic changes in the nasal passages were indicative of minor irritation caused by the test article but were fully healed with no visible sequelae at 15 days. Given these microscopic changes were expected from the absorption enhancing agent, Intravail (dodecyl-maltoside) and due to their low severity, limited distribution, and reversibility, these changes were not considered to be adverse. Based upon the results of this study a NOAEL of 0.8 mg administered as a single intranasal instillation was established in the rat.

While there are published nonclinical studies with epinephrine dosed in various animal models there is no anticipated risk of toxicity in humans at the doses being administered where levels are within the normal endogenous level of the body. In addition, the nonclinical pharmacology, pharmacokinetics, and toxicological profile of epinephrine by the IV, IM, SC, and inhalation routes of administration have been evaluated, are found in the literature, and were part of several approved MAA, NDA, and ANDA applications.

The collective nonclinical data supports an acceptable level of safety for ***neffy*** considering the extensive clinical experience with epinephrine and ARS clinical studies in more than 550 individuals and more than 1069 administrations of ***neffy***, including repeat dosing up to 4 mg.

7.2. Safety of *neffy* in Clinical Studies

Fifteen pharmacokinetic/safety studies were completed with ***neffy*** in healthy volunteers (EPI 03, EPI 06, EPI 07, EPI 11, EPI 11b, and EPI 15), in patients with Type I allergies (EPI 09, EPI 12, EPI 13, EPI 14, and EPI 17), in patients with allergic rhinitis (EPI 04, EPI 16, and EPI JP 01), and pediatric patients with Type I allergies (EPI 10 - study is ongoing at the time of this NDA). These referenced studies were conducted with the commercial formulation of ***neffy***, as well as formulations that contained varied concentrations of the excipient dodecylmaltoside (DDM) (0.25% - 0.35%), which bracket the commercial formulation concentration of DDM (0.275%).

7.2.1. Demographics and Extent of Exposure

7.2.1.1. Extent of Exposure in Pivotal Safety Studies

A cumulative total dosing exposure was evaluated on a study population which consisted of approximately 600 subjects that were enrolled and received at least one dose of ***neffy*** in the studies in primary PK/PD studies EPI 15, EPI 16, EPI 17, and EPI 10 (interim pediatric study); supportive PK/PD studies EPI 03, EPI 04, EPI 07, EPI JP01, EPI 11b, EPI 12, and EPI 14; and the non-supportive PK/PD studies EPI 06, EPI 09, EPI 11, and EPI 13. Due to the crossover design of each study, subjects received more than one exposure to ***neffy*** per study, for a total of 1127 total exposures to ***neffy*** across the fifteen studies.

7.2.1.2. Demographic and Other Characteristics from Primary *neffy* 2 mg Studies (EPI 15, EPI 16, and EPI 17)

In support of the intended commercial dose of ***neffy***, an integrated safety analysis of the primary studies using ***neffy*** 2 mg was also conducted. The 2 mg primary studies safety analysis pools data from studies EPI 15, EPI 16, and EPI 17 and compares the AEs of single dose ***neffy*** (2 mg) and repeat dose ***neffy*** (4 mg) to the injectable epinephrine control arms. The analysis pools the subjects with and without rhinitis. The N size for the analysis is the number of subjects per each treatment received and not the number of exposures (i.e., unique subjects only).

The relevant demographic, baseline, and other characteristics collected from the pooled safety population include age in years, age in groups, sex (gender), races, and ethnicities and are summarized below, as well as in Table 35.

Table 35: Demographic Profile of Patients in Controlled Trials by Pooled Treatment Safety Population - EPI 15, EPI 16, and EPI 17

Demographic	*neffy* Nasal		Epinephrine IM		EpiPen	
	2 mg[1] (N=134) n(%)	4 mg[2] (N=42) n(%)	0.3 mg (n = 134) n(%)	0.5 mg (n = 35) n(%)	0.3 mg (n = 55) n(%)	0.6 mg (L/R)[3] (n = 42) n(%)
Age (Years)						
Mean (SD)	39.5 (9.10)	39.8 (8.98)	39.8 (8.94)	38.1 (8.15)	41.1 (9.68)	39.8 (8.98)
Median	40.0	39.0	40.0	38.0	43.0	39.0
Minimum, Maximum	20,54	25,54	20,54	20,52	22,54	25,54
Sex						
Male	82 (61.2)	30 (71.4)	81 (60.4)	19 (54.3)	37 (67.3)	30 (71.4)
Female	52 (38.8)	12 (28.6)	53 (39.6)	16 (45.7)	18 (32.7)	12 (28.6)
Race						
White	61 (45.5)	20 (47.6)	61 (45.5)	15 (42.9)	32 (58.2)	20 (47.6)
Black or African American	40 (29.9)	15 (35.7)	41 (30.6)	8 (22.9)	16 (29.1)	15 (35.7)
Asian	18 (13.4)	4 (9.5)	17 (12.7)	8 (22.9)	4 (7.3)	4 (9.5)
American Indian or Alaska Native	3 (2.2)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	2 (1.5)	0 (0.0)	2 (1.5)	1 (2.9)	0 (0.0)	0 (0.0)
Other	10 (7.5)	3 (7.1)	10 (7.5)	3 (8.6)	3 (5.5)	3 (7.1)
Ethnicity						
Hispanic or Latino	39 (29.1)	15 (35.7)	40 (29.9)	5 (14.3)	24 (43.6)	15 (35.7)
Not Hispanic or Latino	95 (70.9)	27 (64.3)	94 (70.1)	30 (85.7)	31 (56.4)	27 (64.3)

N = Unique subjects only

[1] *neffy* 2 mg dose includes subjects that received a single 2 mg dose with and without rhinitis.
[2] *neffy* 4 mg dose includes subjects that received two 2 mg doses spaced 10 minutes apart.
[3] EpiPen 0.6 mg includes subjects that received two 0.3 mg doses spaced 10 minutes apart.

7.2.2. Overall Adverse Events Experience

7.2.2.1. Integrated Summary of Safety

The majority of the AEs events that occurred during the clinical trials are consistent with the known AEs for epinephrine and nasal spray applications. No AEs of particular concern were observed.

Increases in blood pressure and heart rate occurred in most subjects and is expected given this is the pharmacological effect of epinephrine and is one of the primary goals when treating an allergic reaction. The effect of epinephrine on the blood pressure and heart rate was a focus of all studies and thus collected and reported as part of safety and efficacy evaluations. Throughout all studies, there was no increase in blood pressure or heart rate that required medical intervention, and the increases were generally mild and resolved quickly.

When considering the intended commercial dose of ***neffy*** 2 mg, the majority of the AEs were mild in severity. A list of moderate and severe events are presented in the Table 36 and Table 37, respectively. All of the severe events shown in Table 37 occurred in the EPI 17 study. All events were resolved within the same day except for headache and vomiting which occurred following Epinephrine 0.3 mg IM injection.

Table 36: List of Moderate Adverse Events

	neffy 2 mg (N=134)	Epinephrine 0.3 mg IM (N=274)	Epinephrine 0.3 mg IM twice (N=70)
Headache	-	2	-
Vomiting	1	1	1
Dizziness	1	-	-
Presyncope	-	1	-
Heart rate decrease	1	-	-
Hypotension	-	1	-

Table 37: List of Severe Adverse Events

	neffy 2 mg (N=134)	Epinephrine 0.3 mg IM (N=274)
Blood pressure decreased	-	1
Asthenia	-	1
Syncope	1	1
Hypotension	1	-

Note: all severe AEs occurred in a single study, EPI 17.

Twice dosing in the ARS primary studies with ***neffy*** 2 mg giving a total dose of 4 mg epinephrine in 10 minutes, resulted in 100% of events being mild and expected for epinephrine. There were no moderate or severe events with ***neffy*** 2 mg given twice. There was 1 moderate event in 1 subject with 0.3 mg IM given twice, which was vomiting.

The remaining AEs in the clinical studies seen were similar between ***neffy*** and the epinephrine injections included in the clinical studies.

There were no clinically meaningful differences in the safety profile of ***neffy*** seen between the studies.

7.2.2.2. Common Adverse Events from *neffy* Primary 2 mg Clinical Trials (Integrated Summary of Safety of EPI 15, EPI 16, and EPI 17)

There were no adverse reactions observed in ≥ 10% of subjects in the ***neffy*** 2 mg treatment group.

Other Adverse Reactions (≥ 1% and < 10%)

Other common adverse reactions that occurred in more than ≥ 2 subjects and observed in ≥ 1% and < 10% of subjects in the ***neffy*** 2 mg group were as follows:

- Nasal discomfort (9.7%)
- Headache (6.0%)
- Rhinorrhea (3.0%)
- Nausea (2.2%)
- Throat irritation (1.5%)
- Dizziness (1.5%)

A display of treatment-related AEs (TEAEs) occurring in >1% frequency and occurrence rates from the pooled primary 2 mg studies is presented by treatment in Table 38.

Table 38: Incidence of Treatment-Related Treatment-Emergent Adverse Events - Pooled Population for EPI 15, EPI 16, and EPI 17

	neffy		Epinephrine IM		EpiPen	
System Organ Class Preferred Term	**2 mg[1] (N=134) n(%)**	**4 mg[2] (N=42) n(%)**	**0.3 mg (n = 134) n(%)**	**0.5 mg (n = 35) n(%)**	**0.3 mg (n = 55) n(%)**	**0.6 mg (L/R)[3] (n = 42) n(%)**
Subjects with at least One Adverse Event	30 (22.4)	6 (14.3)	9 (6.7)	0 (0.0)	2 (3.6)	1 (2.4)
Respiratory, Thoracic and Mediastinal Disorders	**18 (13.4)**	**3 (7.1)**	**1 (0.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Nasal Discomfort	13 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhea	4 (3.0)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Throat Irritation	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	**10 (7.5)**	**4 (9.5)**	**5 (3.7)**	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**
Headache	8 (6.0)	3 (7.1)	3 (2.2)	0 (0.0)	1 (1.8)	0 (0.0)
Dizziness	2 (1.5)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	**3 (2.2)**	**1 (2.4)**	**6 (4.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Nausea	3 (2.2)	0 (0.0)	4 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	**1 (0.7)**	**0 (0.0)**	**2 (1.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Blood Pressure Decreased	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	**1 (0.7)**	**0 (0.0)**	**3 (2.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Hyperhidrosis	1 (0.7)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular Disorders	**1 (0.7)**	**0 (0.0)**	**2 (1.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

	neffy		Epinephrine IM		EpiPen	
System Organ Class Preferred Term	**2 mg[1] (N=134) n(%)**	**4 mg[2] (N=42) n(%)**	**0.3 mg (n = 134) n(%)**	**0.5 mg (n = 35) n(%)**	**0.3 mg (n = 55) n(%)**	**0.6 mg (L/R)[3] (n = 42) n(%)**
Hypotension	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac Disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Palpitations	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)

N = Unique subjects only

Note: MedDRA version 22 used for coding. Events with frequency 1% or greater are reported. Subjects with two or more adverse events in the same system organ class (or with the same preferred term) are counted only once for that system organ class (or preferred term).

[1] ***neffy*** 2 mg dose includes subjects that received a single 2 mg dose with and without rhinitis.
[2] ***neffy*** 4 mg dose includes subjects that received two 2 mg doses spaced 10 minutes apart.
[3] EpiPen 0.6 mg includes subjects that received two 0.3 mg doses spaced 10 minutes apart.

7.2.2.3. Discussion of Adverse Reactions

Based on the integrated analysis from the primary 2 mg studies (EPI 15, EPI 16, and EPI 17), most of the events were mild and no adverse reactions were seen in greater than 10% of the subjects in any treatment group. The most common adverse reaction seen in the ***neffy*** groups including with and without rhinitis were nasal discomfort. The rest of the adverse reactions observed at greater than 1% (and in more than one subject) were headache, rhinorrhea, nausea, throat irritation, and dizziness.

There were a few moderate and severe events reported, which mostly occurred in one subjects and were comparable to injections.

7.2.2.3.1. Pediatric Patients

There are no known differences in the AEs profile in pediatrics versus adults (Simons-1998, Simons-2002). As demonstrated in EPI 10, ***neffy*** 2 mg may be used in persons ≥ 30 kg body weight. During the conduct of EPI 10, there were two moderate TEAEs (nasal discomfort and sneezing following administration of ***neffy*** 2 mg in one subject ≥ 30 kg). All other TEAEs were considered mild, and none were serious, life-threatening, or resulted in death. Adverse events occurring in pediatric subjects are summarized in Table 39.

Currently, the EPI 10 study is complete with the full 21 subjects enrolled in the 30 kg or greater body weight group with ***neffy*** 2 mg. Further, ARS has completed 21 subjects in the 15 to <30 kg group with ***neffy*** 1 mg dose and a supplemental NDA application is planned to be file for this lower dose and lower weight population if current application is approved.

Table 39: Adverse Events Occurring in ≥2 Pediatric Subjects

Preferred Term	*neffy* 0.65 mg (N=12) n(%)	*neffy* 1.0 mg (N=18) n(%)	*neffy* 1.0 mg (N=26) n(%)	*neffy* 2.0 mg (N=21) n(%)
	(15- < 30 kg)		(≥ 30 kg)	
Respiratory, Thoracic and Mediastinal Disorders				
Nasal discomfort	1 (8.3)	1 (5.6)	3 (11.5)	4 (19.0)
Rhinorrhoea	1 (8.3)	1 (5.6)	3 (11.5)	3 (14.3)
Rhinalgia	0 (0.0)	1 (5.6)	2 (7.7)	2 (9.5)
Sneezing	0 (0.0)	0 (0.0)	2 (7.7)	3 (14.3)
Intranasal paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	4 (19.0)
Oropharyngeal pain	0 (0.0)	1 (5.6)	2 (7.7)	1 (4.8)
Throat irritation	2 (16.7)	1 (5.6)	0 (0.0)	1 (4.8)
Epistaxis	1 (8.3)	0 (0.0)	0 (0.0)	2 (9.5)
Dry throat	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)
Nasal congestion	0 (0.0)	1 (5.6)	0 (0.0)	1 (4.8)
Nasal dryness	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)
Nasal mucosal disorder	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)
Pharyngeal paraesthesia	0 (0.0)	0 (0.0)	1 (3.8)	1 (4.8)
Upper-airway cough syndrome	0 (0.0)	1 (5.6)	1 (3.8)	0 (0.0)
Nervous System Disorders				
Paraesthesia	0 (0.0)	2 (11.1)	1 (3.8)	2 (9.5)
Taste disorder	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)
General Disorders and Administration Site Conditions				
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)
Feeling jittery	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)
Eye Disorders				
Lacrimation increased	0 (0.0)	0 (0.0)	2 (7.7)	1 (4.8)
Ocular hyperaemia	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)

7.2.3. Additional Safety Observations from Clinical Trials

7.2.3.1. Nasal Symptoms and Pain

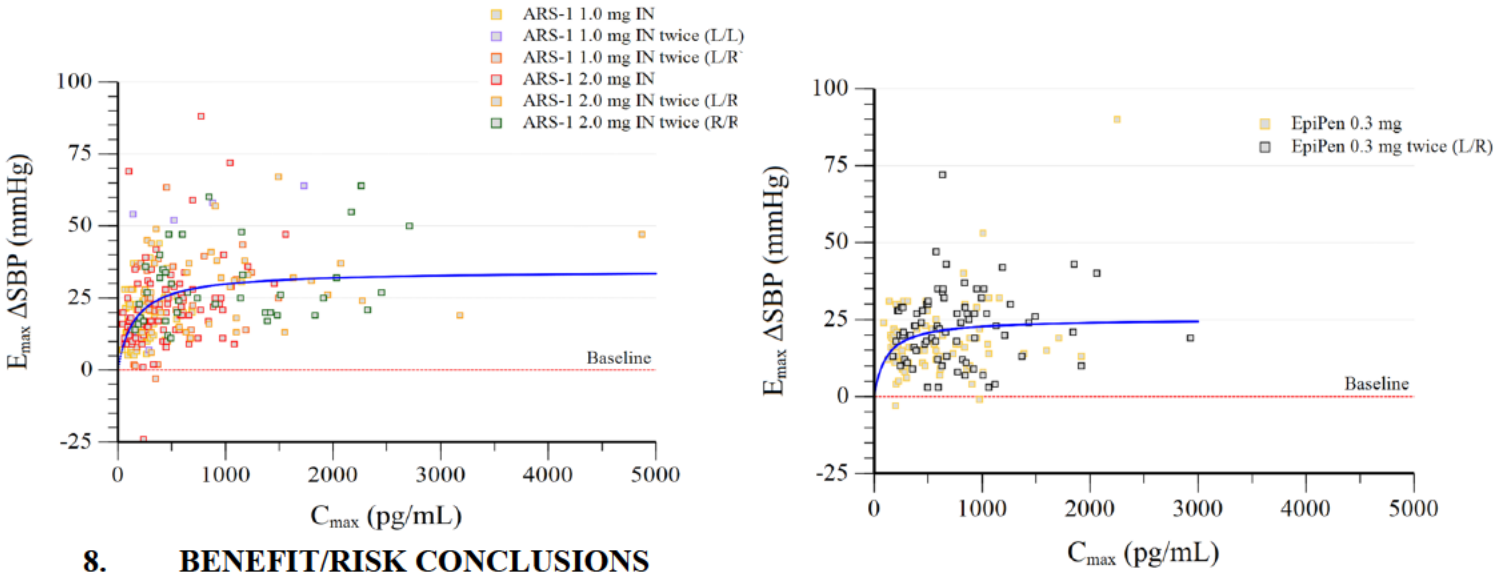
Nasal symptoms, when observed, were generally mild across all treatment groups and doses. Nasal pain was mild with VAS scored 5 mm to 8 mm out of 100 mm in ARS studies.

7.3. C_{max} versus E_{max} Analysis

E_{max} models for the maximum change from baseline SBP versus C_{max} are presented in Figure 33 for ***neffy*** and EpiPen.

Scatter plots from E_{max} model demonstrate maximum increase in SBP at C_{max} of approximately 1000 pg/mL, and that further increase in plasma epinephrine levels did not translate into additional increases unless intra-blood vessel administration as presented in the Section 4.1.

Figure 33: E_{max} Model: neffy and EpiPen, Maximum Change from Baseline Systolic Blood Pressure vs C_{max}



8. BENEFIT/RISK CONCLUSIONS

Symptoms of a Type I allergic reaction are often variable, and it can be difficult to predict severity and rate of progression of an episode. Because the clinical course of anaphylaxis can be unpredictable, prompt and early use of epinephrine should be considered even with mild symptoms or single-system involvement. In the absence of clinical improvement, guidelines for the treatment of anaphylaxis recommend administering repeated doses of epinephrine every 5 to 15 minutes.

Although the importance of early epinephrine treatment has been emphasized in literature and guidelines as well as approved epinephrine labeling or guidelines that instruct dosing immediately after symptoms of an allergic reaction are detected, many patients/caregivers either

do not administer treatment entirely or delay the use of epinephrine autoinjectors (EAIs) until symptoms progress to a more severe state, even when the patient or caregiver knows they are having a severe allergic reaction. These limitations are primarily driven by fear of the needle (needle phobia), concerns about safety, complexity of the device and concerns about having to go to the emergency room (ER) after dosing, often resulting in hesitancy to use the devices, delayed treatment, and an increased risk of serious complications and hospitalizations. As a result of these limitations, a significant proportion of the approximate 25 to 40 million patients at risk of severe Type I allergic reactions in the United States do not receive or fill prescriptions for intramuscular injection products, such as EpiPen or generic equivalents and therefore there is a significant unmet need to address those issues, with a needle-free option.

The pharmacokinetic data from the clinical pharmacology studies demonstrate that a 2 mg dose of ***neffy*** provided exposures that are bracketed by currently approved injection products (higher and more rapid exposures compared to 0.3 mg dose of epinephrine delivered by intramuscular (IM) administration to ensure efficacy and lower exposures than EpiPen 0.3 mg to ensure safety). When administered twice, ***neffy*** resulted in a dose proportional increase in epinephrine concentrations, whereas injection did not give proportional increases in exposure.

The pharmacodynamic results were mostly comparable between ***neffy*** and EpiPen despite the slightly higher and faster pharmacokinetic profile of EpiPen. The smaller drop in the DBP that helped to increase SBP efficiently following ***neffy*** as compared to injection products may be attributed to avoiding injection into the skeletal muscle in the thigh that promotes β_2-mediated vasodilation in and blood flow into the skeletal muscle.

While the mean increases in SBP are greater than that observed with injection, the maximum change in SBP in any individual subject is similar between treatments and there were no indications that the more rapid and greater mean pharmacodynamic effect poses any safety risk to patient experiencing a severe systemic allergic reaction. More likely the more efficient mean pharmacodynamic response of ***neffy*** may represent a potential improved effect based on time to onset, peak response, and a higher proportion of people having a positive hemodynamic response rapidly after administration. This is especially relevant when a second dose is needed due to a more severe event or due to delay in treatment.

Both POP PK and PBAM modeling studies, as well as literature, support that the use of ***neffy*** 2 mg should be acceptable in children aged 12 years or greater who are at least 30 kg body weight.

Both the anaphylaxis dog model and clinical study with induced allergic rhinitis demonstrated that epinephrine absorption with ***neffy*** is increased compared to IM injection for at least the first 15 minutes after administration, which is when the efficacy of a single dose of epinephrine is observed, prior to a second dose being given.

neffy demonstrated acceptable safety profile that were mostly mild and comparable to that of injection products.

Taken together, ***neffy*** demonstrated comparable pharmacokinetic, pharmacodynamic, and safety profile to that of injection products and therefore patients and caregiver would benefit from this easy-to-use and needle-free option when they need emergency treatment. The many patients and caregivers who cannot accept use of a needle-bearing device currently have no other treatment options. ***neffy*** may potentially fill that unmet medical need.

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Appendix 1: EpiPen Study Results Compared to Neffy

neffy PK is Also Bracketed by EpiPen studies (Cmax)

Treatment	Study Reference	N	Mean Study C_{max} (pg/mL)	Median Study T_{max} (min)	T_{max} range (min)	Administration
EpiPen (0.3 mg)	AQST-109 EPIPHAST II Results (2022)	22	869	22	5 to 40	HCP
EpiPen (0.3 mg)	ARS EPI-JP01 Data (2020)	30	676	10	2 to 45	HCP
EpiPen (0.3 mg)	ARS EPI-15 (2022)	35	612	8	2 to 45	HCP
EpiPen (0.3 mg)	Tal et al. EAACI (2022)	12	550	9	n.d.	HCP
EpiPen (0.3 mg)	ARS EPI-11b Data (2021)	9	537	6	2 to 6	HCP
EpiPen (0.3 mg)	Edwards et al. NDA #201739 (2012)	67	520	10.2	4 to 60	HCP
EpiPen (0.3 mg)	Chen et al. AAAAI (2019)	11	511	5	3 to 50	HCP
EpiPen (0.3 mg)	ARS EPI-12 Data (2021)	36	493	8	3 to 154	Self-Admin
EpiPen (0.3 mg)	ARS EPI-13 Data (2022)	39	490	6	2 to 240	Self-Admin
neffy (2.0 mg)	ARS EPI-16 data (2022)	36	491	20	2 to 120	HCP
neffy (2.0 mg)	**ARS integrated analysis (2022)**	**78**	**485**	**20.5**	**2 to 150**	**HCP**
neffy (2.0 mg)	ARS EPI-15 data (2022)	42	481	30	6 to 150	HCP
neffy (2.0 mg)	ARS EPI-17 data (2022)	42	421	30	6 to 240	Self-Admin
EpiPen (0.3 mg)	Worm et al. Clin Transl Allergy (2020)[2]	12	390 to 530	9 to 30	3 to 120	HCP
EpiPen (0.3 mg)	Turner et al. Clin Exp Allergy (2021)[3]	37	386	40	3 to 90	HCP
EpiPen (0.3 mg)	Amphastar US2021/030502 (2021)[1]	56	364 - 458	7 - 15	n.d.	HCP
EpiPen (0.3 mg)	ARS EPI-07 Data (2019)	35	375	24	4 to 45	HCP
EpiPen (0.3 mg)	Dworaczyk et al. AAAAI (2020)[1]	55	308 to 440	10 - 16	1 to 61	HCP
EpiPen (0.3 mg)	Oppenheimer et al. AAAAI (2022)	10	341	22	5 to 90	HCP
EpiPen (0.3 mg)	ARS EPI-01 Data (2018)	12	333	20	6 to 45	HCP
EpiPen (0.3 mg)	Aquestive R&D Day (2021)	9	300	10[4]	n.d.	HCP
EpiPen (0.3 mg)	Dworaczyk et al. AAAAI (2021)	25	288	10	5 to 90	HCP