Neffy Profile and Registrational Program

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ARS PHARMA

neffy is a High Bioavailability, Low 2 mg Dose Saline-Based Nasal Spray: Proven Triad of FDA-Approved Components

High bioavailability with low dose minimizes side effects that mimic anaphylaxis (GI symptoms) and risk of cardiotoxicity from overdosing

> 9 FDA Approvals in Allergy
(> 100 years of clinical experience)

3 FDA Approvals incl. Intravail
(> 1 million Rx)[1]

TOSYMRA® VALTOCO®

OPVEE®

Epinephrine

Intravail®
dodecyl-maltoside: GRAS absorption enhancer

Sprayer

7 FDA Approvals of Sprayer
(> 55 million Rx, 99.999% reliable)[1]

NARCAN®

VALTOCO®

NAYZILAM®

IMITREX®

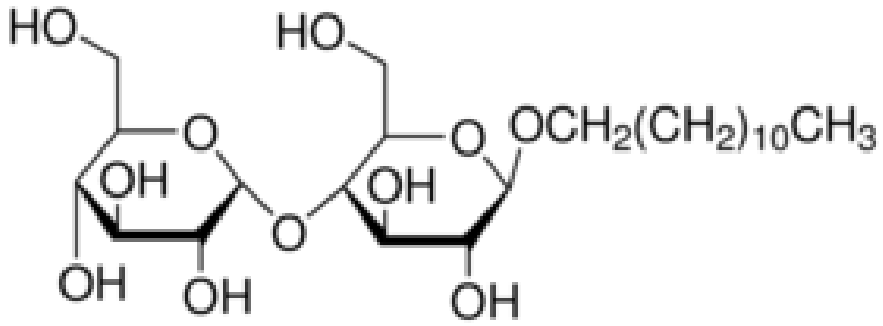
TOSYMRA®

ZAVZPRET®

OPVEE®

References: 1. IQVIA Prescription data, and ARS company data on file

Intravail® Allows Injection-Like PK at a Low Intranasal Dose Without Irritation or Pain, and Robust IP Protection to 2038+



n-Dodecyl beta-D-maltoside (Intravail®)

- Generally recognized as safe (GRAS) absorption enhancing agent
- Biologic surfactant that loosens tight junctions (paracellular) coupled with fluidization and penetration of cell membranes (transcellular)
- **No irritation, pain or damage to nasal mucosa**
- Extensive toxicology and safety program

NCE-like exclusivity enabled by Intravail

- **No systemic absorption via nose without Intravail** when epinephrine is put in water-based solution
- Intravail allows systemic intranasal absorption of epinephrine within the known therapeutic dose window for injection products
- **No inhalation required – absorption in nasal mucosa**
- **Issued composition of matter patents in the US and globally covering Intravail® + epinephrine[1, 2]**
- **Issued method of treatment patents blocks other low dose aqueous nasal sprays (<4 mg dose)[3-7]**
- **Exclusivity until at least 2038 without PTE**

References: 1. US10,576,156, **2.** US11,173,209, **3.** US10,682,414, **4.** US11,191,838, **5.** US11,744,895, **6.** US11,717,571, **7.** US11,918,655

Designed for Easier Carry and Portability

Case holds two neffy 2mg devices.

Basis of Approval for Community Use Products

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

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

All Products Demonstrate Efficacy Despite Different PK

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

Treatment[1]	Source	N	Mean Study C_{max} (pg/mL)	Median or Mean Study T_{max} (min)	Study T_{max} Range (min)
EpiPen 0.3 mg	Literature and ARS	507	288 – 869	5 to 40	1 – 240
IM 0.3 mg	Literature and ARS	381	209 – 489	30 to 60	3 – 360
Auvi-Q 0.3 mg	Literature	96	486 – 646	20 to 30	5 – 60
Symjepi 0.3 mg	ARS data	88	337 – 438	30	4 – 240
SC 0.3 mg	ARS	36	246	45	4 – 180
Total Range			**209 to 869**	**5 to 60**	**1 to 360**

References: 1. Srisiwat C, et al. *Asian Pac J Allergy Immunol*. 2022. **2.** Aquestive Therapeutics Press Release. Sept 2022. **3.** Edwards ES, et al. *Ann Allergy Asthma Immunol*. 2013. **4.** Dworaczyk D & Hunt A. Abstract Presentation AAAAI 2021 (Virtual Meeting). **5.** Aquestive Therapeutics Press Release. May 2023.

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

PK to ensure efficacious and safe exposures within range of approved products - Bracketing Approach

- Minimum exposure $\geq$ IM/SC (efficacy)
- Maximum exposures < EpiPen (safety)

PD response to support effect at achieving receptor response

- Blood pressure (BP): α_1 & β_1 (β_2) receptors
- Heart rate (HR): β_1 receptors

Registrational Studies Demonstrate Comparability on Both PD Surrogates for Efficacy and PK with *neffy*

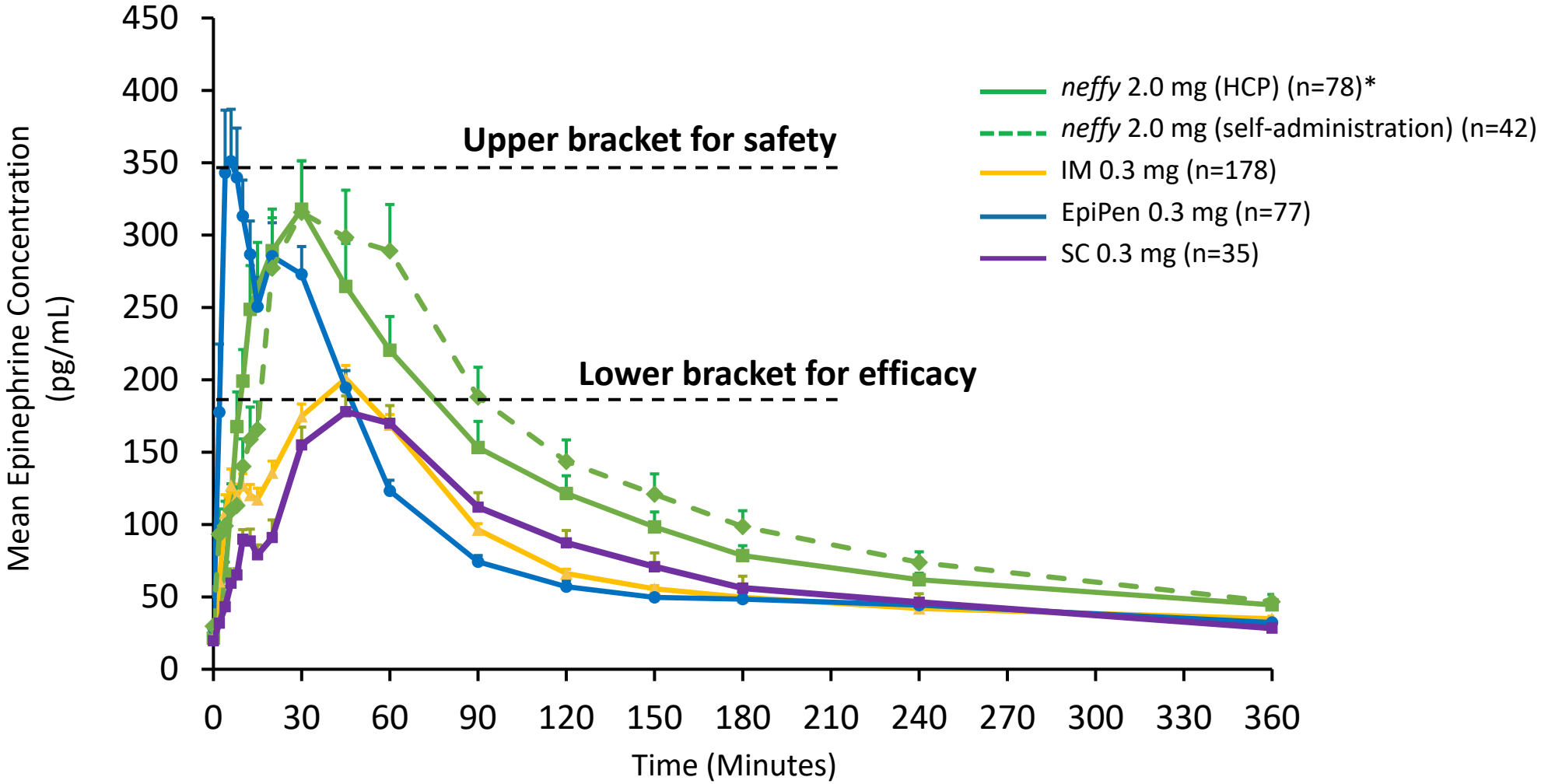
PD and PK Data

- 2 mg *neffy* met all clinical endpoints
- PD surrogates for efficacy comparable to approved products (SBP/HR ≥ approved injection products)
- Rapid and significant response on PD surrogates for efficacy observed even 1 minute after dosing
- PK bracketed by approved products (exposures ≥ IM/SC for efficacy, < EpiPen for safety)
- Repeat doses (including during rhinitis) within range of approved injection products

Safety Data

- Adverse events generally mild in nature with no meaningful nasal irritation or pain up to 4 mg dose
- Most common adverse events (>5%) were mild nasal discomfort (9.7%) and mild headache (6%), with no correlation of nasal discomfort to pain or irritation
  - Mean VAS pain scores between 5 to 8 out of 100
  - No irritation based on formal assessment
- No serious adverse events in any clinical study
- No risk of needle-related injuries or blood vessel injections with *neffy*

Pharmacokinetic Results from *neffy* 2 mg Studies Satisfies Bracketing Approach designed with FDA

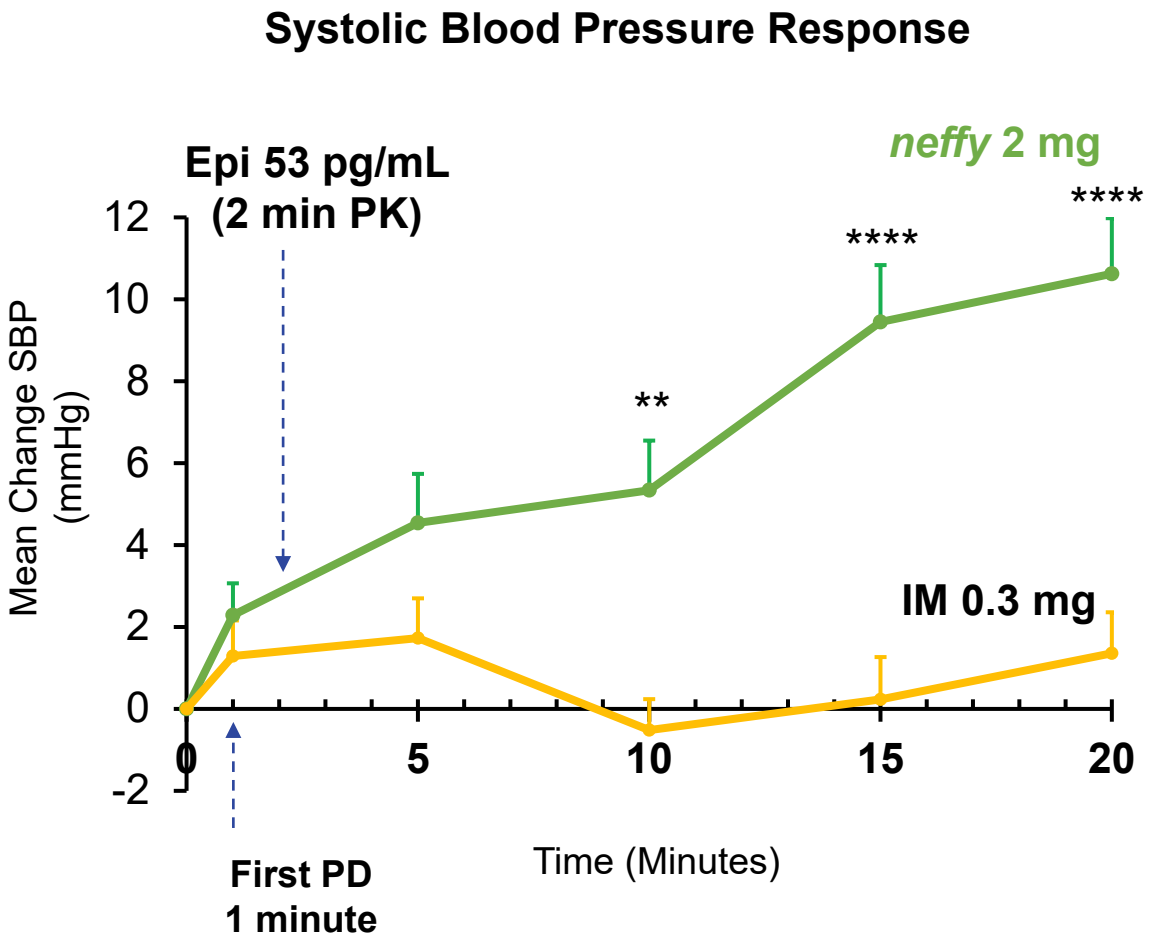


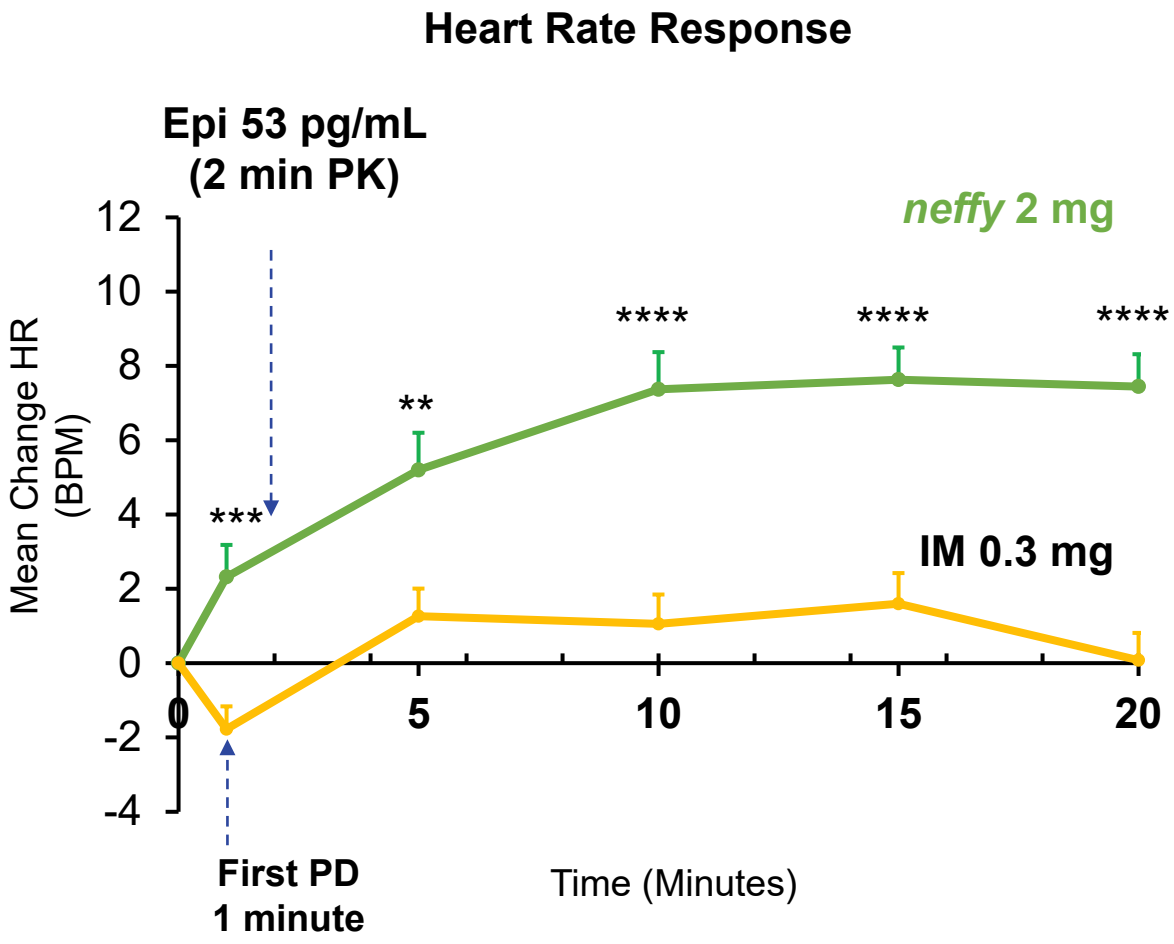
*Includes Studies EPI-15 and EPI-16

neffy PK is Bracketed by EpiPen Studies (Cmax or tmax)

Treatment	Study Reference	N	Mean Study C_{max} (pg/mL)	Median Study T_{max} (min)
EpiPen (0.3 mg)	AQST-109 EPIPHAST II Results (2022)	22	869	22
	ARS EPI-JP01 Data (2020)	30	676	10
	AQST-109 Pilot Results (2023)	27	628	10
	ARS EPI-15 (2022)	35	612	8
	Tal et al. EAACI (2022)	12	550	9
	ARS EPI-11b Data (2021)	9	537	6
	Edwards et al. NDA #201739 (2012)	67	520	10.2
	Chen et al. AAAAI (2019)	11	511	5
	ARS EPI-12 Data (2021)	36	493	8
	ARS EPI-13 Data (2022)	39	490	6
***neffy* (2.0 mg)**	ARS EPI-16 data (2022)	36	491	20
	ARS integrated analysis (2022) – EPI-15/16	**78**	**485**	**20.5**
	ARS EPI-15 data (2022)	42	481	30
	ARS EPI-17 data (2022)	42	421	30
EpiPen (0.3 mg)	Worm et al. Clin Transl Allergy (2020)	12	390 to 530	9 to 30
	Turner et al. Clin Exp Allergy (2021)	37	386	40
	Amphastar US2021/030502 (2021)	56	364 - 458	7-15
	ARS EPI-07 Data (2019)	35	375	24
	Dworaczyk et al. AAAAI (2020)	55	308 to 440	10-16
	Oppenheimer et al. AAAAI (2022)	10	341	22
	ARS EPI-01 Data (2018)	12	333	20
	Aquestive R&D Day (2021)	9	300	10
	Dworaczyk et al. AAAAI (2021)	25	288	10
	Dworaczyk et al. ACAAI (2023)	26	279	20
	Dworaczyk et al. ACAAI (2023)	25	228	21

Robust Response on PD Surrogate Markers for Efficacy





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

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

Positive FDA AdCom vote supports benefit-risk of *neffy*

FDA Advisory Committee (May 2023) voted that benefit-risk of *neffy* supported FDA approval

- 17:5 and 16:6 voted in favor for approval in pediatric and adult populations, respectively
- Advisory members who voted against approval desired comparative clinical efficacy data for anaphylaxis, which cannot be ethically conducted in this population

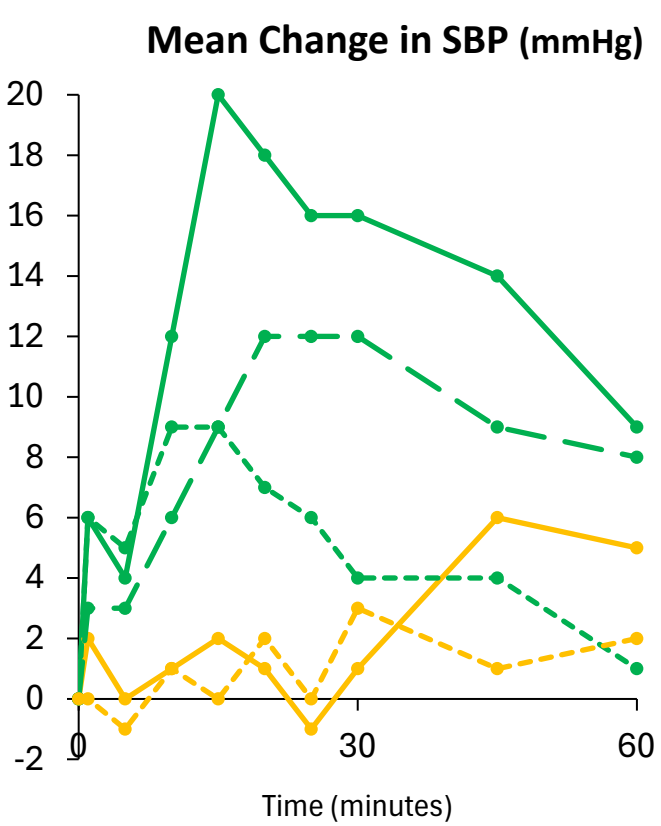
FDA Advisory Committee viewed single dose NAC study data as "encouraging" and "favorable" due to greater concentration levels during the period when clinical response is observed with epinephrine

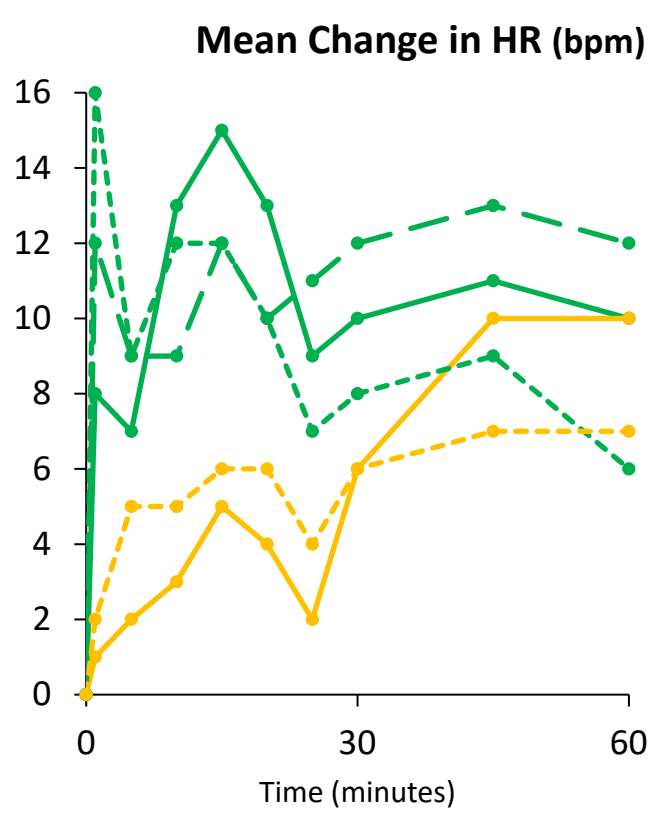
- Nasal congestion following nasal-allergen challenge (spraying purified antigen directly into the nose) accelerates absorption of *neffy* in the first 20 minutes vs. normal state
- Treatment guidelines recommend giving a second dose if no response is observed within 5 to 15 minutes of administration
- FDA reported that the rate of nasal mucosal symptoms in anaphylaxis patients ranges from 2 to 11% *(weighted average frequency in the literature is ~4% based on aggregated analysis of 13 publications)*

No member of the Advisory Committee requested a repeat dose rhinitis study as a prerequisite for FDA approval

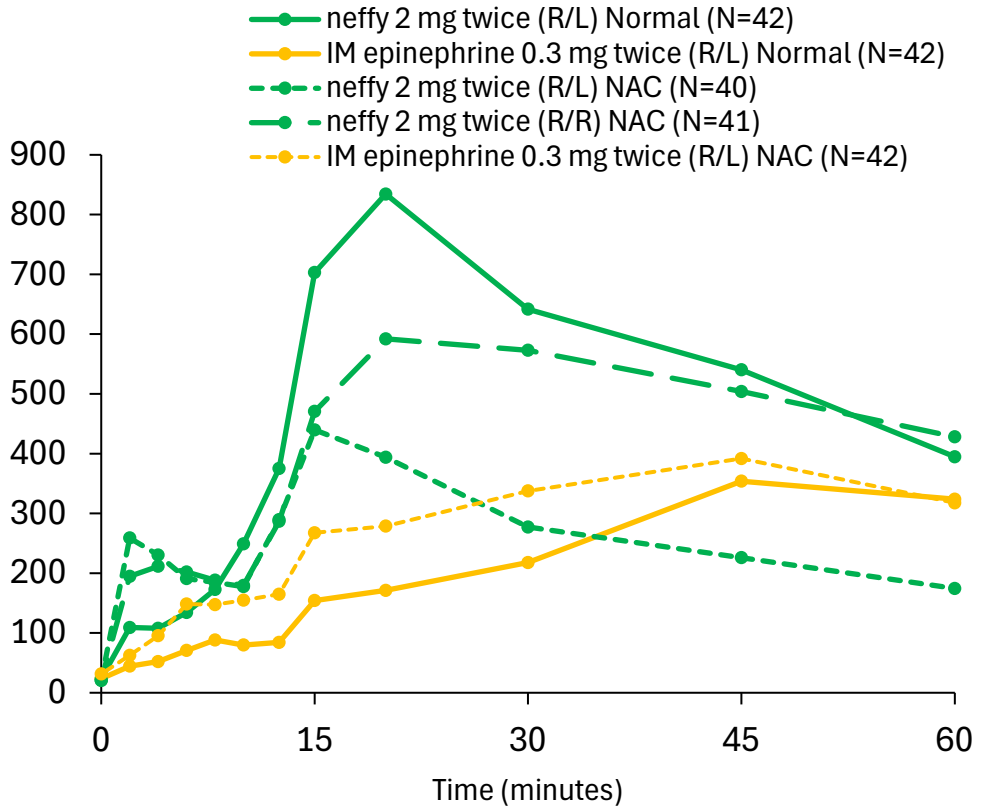
Completion of Repeat Dose *neffy* NAC study per FDA's CRL Request Shows PK/PD Greater or Similar to IM Injection

PD Response (Mean Change in SBP, HR)





PK Profile (Mean Plasma Concentrations, pg/mL)



Response to FDA's CRL anticipated by early Q2 2024 followed by up to 6-month FDA review

Note: FDA explicitly requested IM epinephrine as the comparator in this study because IM is the basis for efficacy for epinephrine products, and there are no known differences between the various approved injection devices despite different PK