

# ARS-1 (neffy® Nasal Spray) 2.0 mg Versus Epinephrine Injection Products: An Integrated Pharmacokinetic Analysis

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## RATIONALE

International guidelines agree that rapid intramuscular (IM) administration of epinephrine to the anterolateral thigh should be the first line treatment for severe allergic reactions and anaphylaxis.<sup>1,2</sup>

While all the approved Epinephrine Auto-Injectors (EAI) are considered effective for the treatment of severe allergic reactions and anaphylaxis, they are also considered inconvenient and cumbersome. Up to 83% of patients/caregivers fail to administer treatment or delay the use of EAI even when they know they are having a severe allergic reaction.<sup>3,4,5</sup> Reasons for hesitation to the use of EAI include high costs, failure to carry the device, failure to recognize a severe allergic reaction, and lack of proper training on how to use the device.<sup>6,7,8</sup>

**neffy** is an intranasal (IN) epinephrine spray that is a needle-free alternative epinephrine delivery device being developed for the emergency treatment of (Type I) allergic reactions, including anaphylaxis. **neffy** is expected to have significant clinical benefit by reducing apprehension and delay in dosing, reducing dosing errors, and making it easier to carry the product at all times.

This integrated analysis was conducted to analyze the pharmacokinetics (PK) and pharmacodynamics (PD) of a 2.0 mg dose of **neffy** relative to both manual IM injection and EpiPen®.

## METHODS

An integrated PK and PD analysis was conducted using data from five randomized, open-label, phase 1 trials that compared the pharmacokinetic and pharmacodynamic profiles of **neffy** 2.0 mg IN spray with manual IM Epinephrine (0.3 mg and 0.5 mg) and EpiPen 0.3 mg.

Three studies enrolled healthy individuals aged 19 to 55 years, and two studies enrolled healthy volunteers with a history of Type I allergies (allergic rhinitis, food allergy, venom allergy), aged 19 to 55 years.

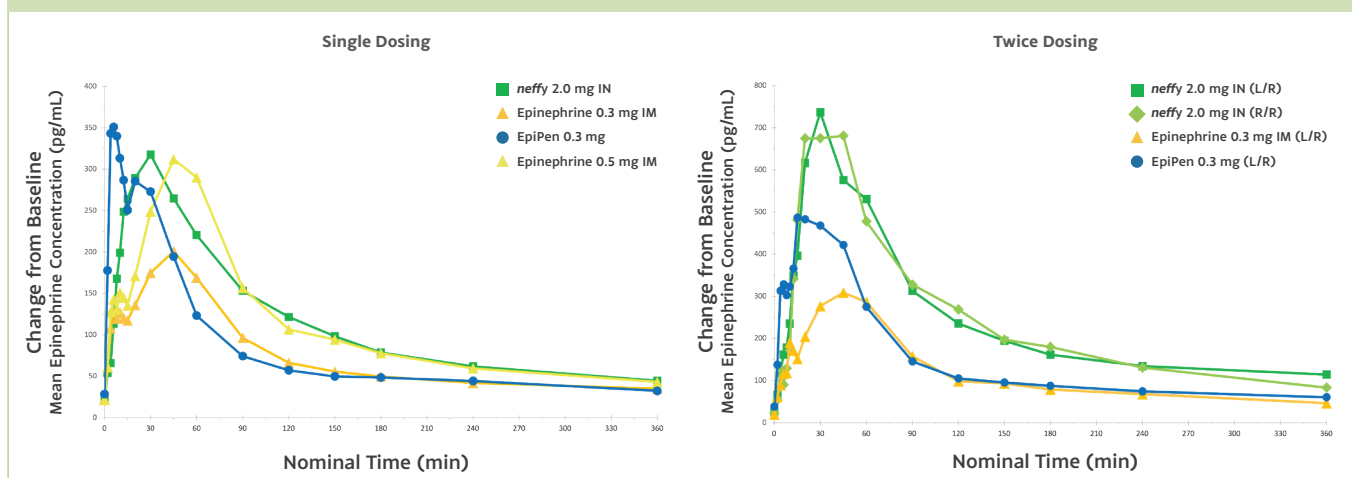
For **neffy** 2.0 mg, Epinephrine 0.3 mg IM, and EpiPen 0.3 mg (but not for epinephrine 0.5 mg), both single and twice dosings (two doses spaced 10 minutes apart) were investigated. When **neffy** was administered twice, it was done with two doses to the same nare ([R/R]) or two doses to opposite nares ([L/R]).

## RESULTS: PHARMACOKINETIC

### Concentration vs Time (Figure 1)

For both single and twice dosed treatments, **neffy** 2.0 mg resulted in mean epinephrine plasma concentrations that fell between the currently approved injection products. Until approximately 25 minutes post-dose, plasma epinephrine levels were higher following **neffy** 2.0 mg relative to Epinephrine 0.5 mg IM.

Figure 1: Change from Baseline - Mean Epinephrine Concentration versus Time Profiles by Treatment



## Pharmacokinetic Parameters (Table 1)

### $C_{max}$

Mean  $C_{max}$  values following single dosing were highest after EpiPen 0.3 mg (581 pg/mL), followed by **neffy** 2.0 mg (485 pg/mL), Epinephrine 0.5 mg IM (399 pg/mL), and Epinephrine 0.3 mg IM (277 pg/mL).

Mean  $C_{max}$  values following twice dosing were highest after **neffy** 2.0 mg twice [L/R] (1000 pg/mL) and **neffy** 2.0 mg twice [R/R] (922 pg/mL), followed by EpiPen 0.3 mg twice (754 pg/mL), and Epinephrine 0.3 mg IM twice (436 pg/mL).

### $t_{max}$

Median  $t_{max}$  values following single dosing were shortest after EpiPen 0.3 mg (10 minutes), followed by **neffy** 2.0 mg (20.5 minutes), and Epinephrine 0.3 mg and 0.5 mg IM (45 minutes).

Median  $t_{max}$  values following twice dosing were shortest after EpiPen 0.3 mg twice (20 minutes), followed by **neffy** 2.0 mg twice [L/L], **neffy** 2.0 mg twice [L/R], **neffy** 2.0 mg twice [R/L] (30 minutes each), and Epinephrine 0.3 mg IM twice (45 minutes).

### AUC

The greatest total exposure following single dosing was observed after Epinephrine 0.5 mg IM (43700 min\*pg/mL), followed by **neffy** 2.0 mg (40900 min\*pg/mL), EpiPen 0.3 mg (31600 min\*pg/mL), and Epinephrine 0.3 mg (27900 min\*pg/mL).

The greatest total exposure following twice dosing was observed after **neffy** 2.0 mg twice [R/R] (86500 min\*pg/mL), followed by **neffy** 2.0 mg twice [L/R] (86000 min\*pg/mL), EpiPen 0.3 mg IM twice (55000 min\*pg/mL), and Epinephrine 0.3 mg IM twice (47500 min\*pg/mL).

**Table 1: Epinephrine Pharmacokinetic Parameters by Treatment**

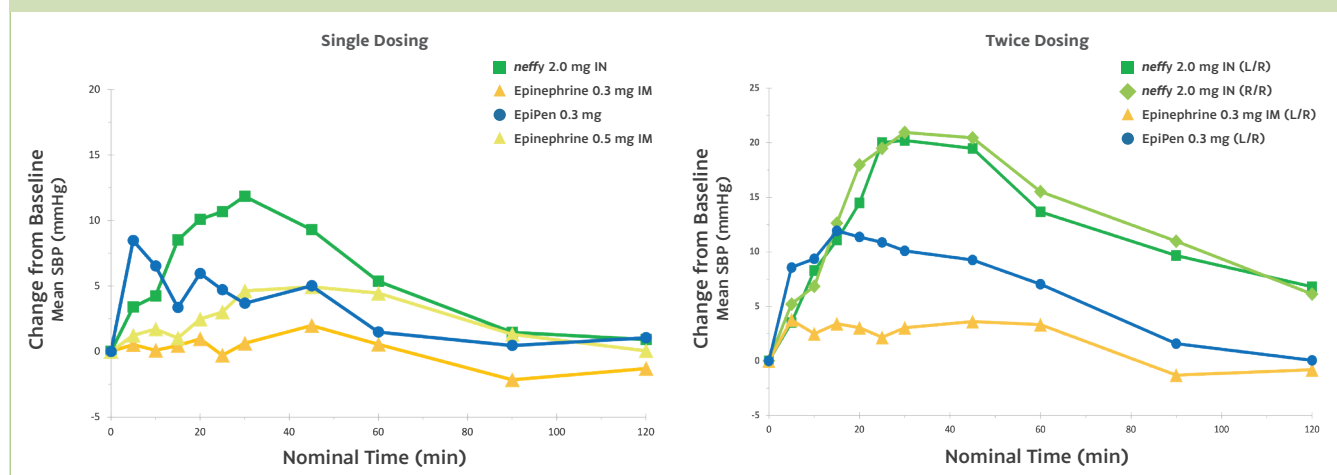
Treatment	N	$t_{max}$ (min) median (range)	$C_{max}$ (pg/mL) mean (%CV)	AUC <sub>last</sub> (min*pg/mL) mean (%CV)
<b>Single Dosing</b>				
<b>neffy 2.0 mg IN</b>	<b>78</b>	<b>20.5 (2 - 150)</b>	<b>485 (70.6)</b>	<b>40900 (67.5)</b>
<b>Epinephrine 0.3 mg IM</b>	<b>178</b>	<b>45 (3.9 - 360)</b>	<b>277 (65.4)</b>	<b>27900 (38.7)</b>
<b>EpiPen 0.3 mg</b>	<b>77</b>	<b>10 (2 - 45)</b>	<b>581 (75.6)</b>	<b>31600 (39.3)</b>
<b>Epinephrine 0.5 mg IM</b>	<b>123</b>	<b>45 (4 - 360)</b>	<b>399 (65.5)</b>	<b>43700 (34)</b>
<b>Twice Dosing</b>				
<b>neffy 2.0 mg IN (L/R)</b>	<b>39</b>	<b>30 (6 - 150)</b>	<b>1000 (93.1)</b>	<b>86000 (77)</b>
<b>neffy 2.0 mg IN (R/R)</b>	<b>39</b>	<b>30 (4 - 150)</b>	<b>922 (75.3)</b>	<b>86500 (60.5)</b>
<b>Epinephrine 0.3 mg IM (L/R)</b>	<b>70</b>	<b>45 (6 - 180)</b>	<b>436 (48.8)</b>	<b>47500 (32.6)</b>
<b>EpiPen 0.3 mg (L/R)</b>	<b>78</b>	<b>20 (4 - 360)</b>	<b>754 (64.7)</b>	<b>55000 (47.9)</b>

## RESULTS: PHARMACODYNAMIC

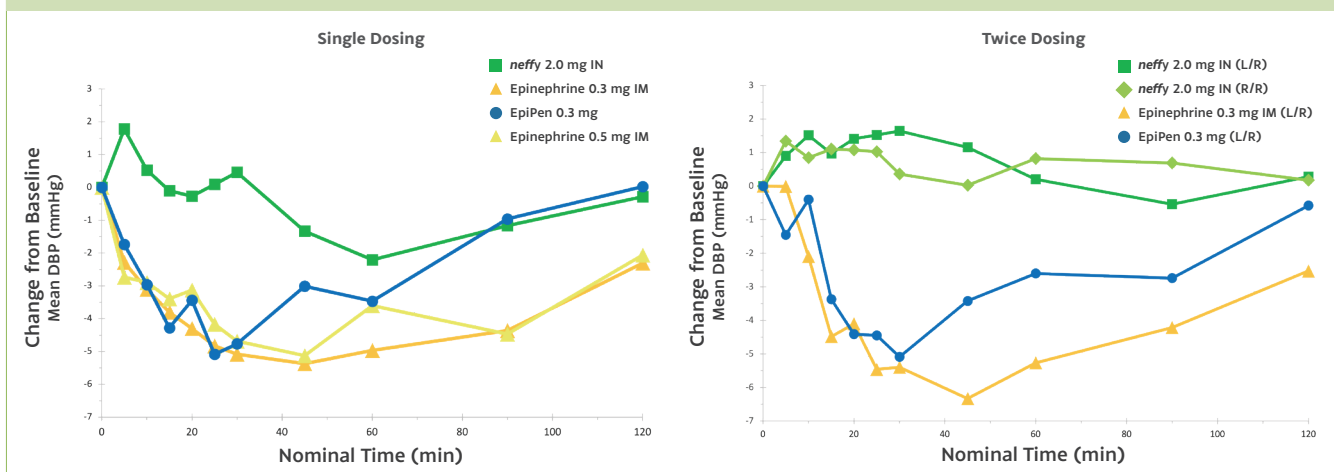
### Change from Baseline vs Time

In general, **neffy** 2.0 mg IN resulted in pharmacodynamic responses that were comparable to or better than injection products (Figure 2, Figure 3, and Figure 4).

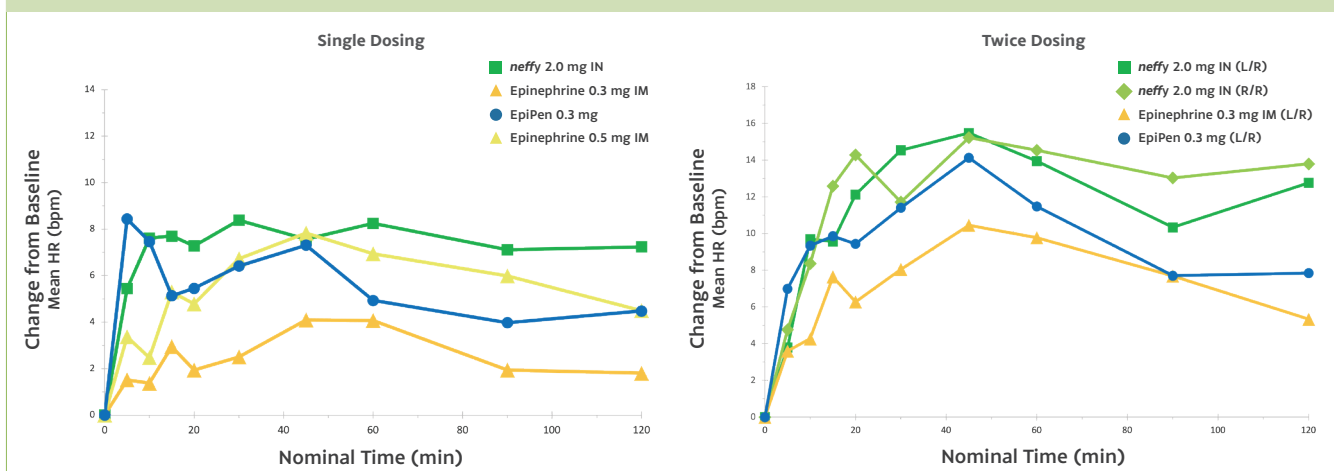
**Figure 2: Change from Baseline - Mean Systolic Blood Pressure (SBP) versus Time Profiles by Treatment**



**Figure 3: Change from Baseline - Mean Diastolic Blood Pressure (DBP) versus Time Profiles by Treatment**



**Figure 4: Change from Baseline - Mean Heart Rate (HR) versus Time Profiles by Treatment**



Pharmacodynamic Parameters (Table 2)

**Systolic Blood Pressure (SBP)**

**SBP  $E_{max}$**

Mean SBP  $E_{max}$  values following single dosing were highest after **neffy** 2.0 mg (22.3 mmHg), followed by EpiPen 0.3 mg (18.2 mmHg), Epinephrine 0.5 mg IM (13.6 mmHg), and Epinephrine 0.3 mg IM (11.6 mmHg).

Mean SBP  $E_{max}$  values following twice dosing were highest after **neffy** 2.0 mg twice [R/R] (29.1 mmHg), **neffy** 2.0 mg twice [L/R] (28.9 mmHg), EpiPen 0.3 mg twice (22.6 mmHg), and Epinephrine 0.3 mg IM twice (13.4 mmHg).

**SBP  $t_{Emax}$**

Median SBP  $t_{Emax}$  values following single dosing were shortest after EpiPen 0.3 mg (16 minutes), followed by **neffy** 2.0 mg and Epinephrine 0.3 mg IM (25 minutes each), and Epinephrine 0.5 mg (30.5 minutes).

Median SBP  $t_{Emax}$  values following twice dosing were shortest after EpiPen 0.3 mg twice (19 minutes), followed by Epinephrine 0.3 mg IM twice (21.5 minutes), **neffy** 2.0 mg twice [R/R] (28 minutes), and **neffy** 2.0 mg twice [L/L] (29 minutes).

**Diastolic Blood Pressure (DBP)**

**DBP  $E_{max}$**

Mean DBP  $E_{max}$  values following single dosing were highest after **neffy** 2.0 mg (8.99 mmHg), followed by EpiPen 0.3 mg (6.48 mmHg), Epinephrine 0.5 mg IM (5.81mmHg), and Epinephrine 0.3 mg IM (5.44 mmHg).

Mean DBP  $E_{max}$  values following twice dosing were highest after **neffy** 2.0 mg twice [L/R] (10.5 mmHg), neffy 2 mg twice [R/R] (9.62 mmHg), EpiPen 0.3 mg twice (7.35 mmHg), and Epinephrine 0.3 mg IM twice (6.04 mmHg).

### DBP $t_{E_{max}}$

Median DBP  $t_{E_{max}}$  values following single dosing were shortest after Epinephrine 0.3 mg IM (9 minutes), followed by Epinephrine 0.5 mg (17 minutes), **neffy** 2.0 mg (19 minutes), and EpiPen 0.3 mg (21 minutes).

Median DBP  $t_{E_{max}}$  values following twice dosing were shortest after Epinephrine 0.3 mg IM twice (5 minutes), followed by **neffy** 2.0 mg twice [R/R] (13 minutes), EpiPen 0.3 mg twice (16 minutes), and **neffy** 2.0 mg twice [L/R] (19 minutes).

### Heart Rate (HR)

#### HR $E_{max}$

Mean HR  $E_{max}$  values following single dosing were highest after **neffy** 2.0 mg (17.8 bpm), followed by EpiPen 0.3 mg (14.8 bpm), Epinephrine 0.5 mg IM (14.5 bpm), and Epinephrine 0.3 mg IM (11.5 bpm).

Mean HR  $E_{max}$  values following twice dosing were highest after **neffy** 2.0 mg twice [R/R] (22.9 bpm), followed by **neffy** 2.0 mg twice [L/R] (22.1 bpm), EpiPen 0.3 mg (19.8 bpm), and Epinephrine 0.3 mg IM twice (17 bpm).

### HR $t_{E_{max}}$

Median HR  $t_{E_{max}}$  values following single dosing were shortest after EpiPen 0.3 mg (17 minutes), **neffy** 2.0 mg (19.5 minutes), Epinephrine 0.3 mg IM (29.5 minutes), and Epinephrine 0.5 mg (44.5 minutes).

Median HR  $t_{E_{max}}$  values following twice dosing were shortest after **neffy** 2.0 mg twice [L/R] and EpiPen 0.3 mg twice (29 minutes), followed by **neffy** 2.0 mg twice [R/R] (40 minutes), and Epinephrine 0.3 mg IM twice (44.9 minutes).

### Safety Results

Safety results were not included in the integrated pharmacokinetic/pharmacodynamic analysis; however, the individual results of these five trials demonstrate that **neffy** is safe and well tolerated, with an adverse events profile comparable to those observed with the approved injection products.

Table 2: Epinephrine Pharmacodynamic Parameters by Treatment

Treatment	N	$E_{max}$ mean (%CV)			$t_{max}$ median (range)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
<b>Single Dosing</b>							
<b>neffy 2.0 mg IN</b>	78	22.3 (71.5)	8.99 (72.6)	17.8 (69.3)	25 (1 - 120)	19 (1 - 120)	19.5 (1 - 120)
<b>Epinephrine 0.3 mg IM</b>	142	11.6 (73.8)	5.44 (125)	11.5 (69.7)	25 (0.97 - 120)	9 (0.97 - 120)	29.5 (1 - 120)
<b>EpiPen 0.3 mg</b>	77	18.2 (67.9)	6.48 (112)	14.8 (60.8)	16 (1 - 119)	21 (1 - 119)	17 (1 - 115)
<b>Epinephrine 0.5 mg IM</b>	100	13.6 (74)	5.81 (122)	14.5 (60.2)	30.5 (0.93 - 120)	17 (0.92 - 120)	44.5 (1 - 120)
<b>Twice Dosing</b>							
<b>neffy 2.0 mg IN (L/R)</b>	39	28.9 (47)	10.5 (71.2)	22.1 (55)	29 (2 - 116)	19 (1 - 115)	29 (1 - 116)
<b>neffy 2.0 mg IN (R/R)</b>	39	29.1 (46)	9.62 (83.5)	22.9 (44.3)	28 (6 - 85)	13 (1 - 118)	40 (1 - 116)
<b>Epinephrine 0.3 mg IM (L/R)</b>	70	13.4 (71.1)	6.04 (116)	17 (45.2)	21.5 (0.97 - 120)	5 (0.82 - 120)	44.9 (1.97 - 120)
<b>EpiPen 0.3 mg (L/R)</b>	78	22.6 (51.7)	7.35 (109)	19.8 (50.3)	19 (1 - 88)	16 (1 - 119)	29 (1 - 119)

## DISCUSSION

- The results of this integrated analysis of five clinical studies demonstrates that **neffy** 2.0 mg has a PK profile that is within the range of currently approved injection products (Epinephrine 0.3 mg IM and EpiPen 0.3 mg).
- Based on  $C_{max}$ , **neffy** 2.0 mg appeared to be relatively dose proportional between once dose and twice dosing, while Epinephrine 0.3 mg IM and EpiPen 0.3 mg was less than dose proportional.
- neffy**'s PD profile is comparable to or better than both Epinephrine 0.3 mg IM and EpiPen 0.3 mg, suggesting that **neffy** may be at least as efficacious as the approved products.
- The safety results of the individual studies demonstrate that **neffy** is safe and well tolerated, with adverse events comparable to those observed with the approved injection products.

## CONCLUSION

**neffy**'s PK profile is within the range of approved epinephrine injection products and its PD profile is comparable to or better than both IM Epinephrine and EpiPen. Taken together, these findings suggest that **neffy** has the potential to be an additional option for the first line treatment of (Type I) allergic reactions, including anaphylaxis.

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