# 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 (EAIs) 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 EAIs even when they know they are having a severe allergic reaction.<sup>3,4,5</sup> Reasons for hesitation to the use of EAIs 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. 6,7,8

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 RESULTS (Figure 1 and Table 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.

#### PHARMACODYNAMIC RESULTS (Table 2)

In general, neffy 2.0 mg resulted in pharmacodynamic responses that were comparable to injection products. For SBP, DBP and HR, the highest  $E_{max}$  values were observed following neffy 2.0 mg.

## 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.

#### CONCLUSION

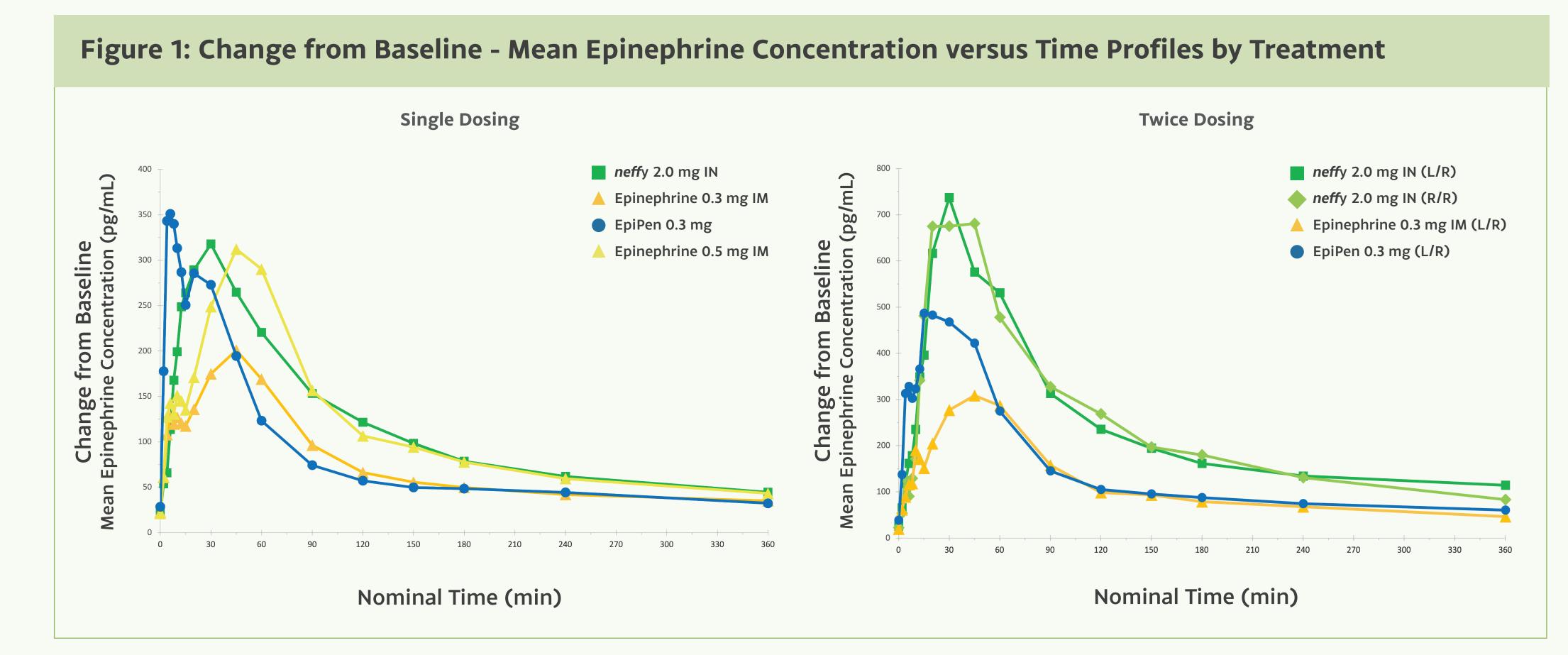
- The results of this integrated analysis of five clinical studies demonstrates that neffy 2.0 mg has a PK profile that is within the range of currently approved injection products.
- •neffy's PD profile is comparable to or better than both Epinephrine 0.3 mg IM and EpiPen 0.3 mg, suggesting that *neffy* may be at least as efficacious as the approved products.
- Based on C<sub>max</sub>, neffy appeared to be relatively dose proportional between once dose and twice dosing, while Epinephrine 0.3 mg IM and EpiPen 0.3 mg did not appear to be dose proportional.
- 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.

# This Integrated Analysis Demonstrates:

- neffy's PK profile is within the range of approved epinephrine injection products.
- neffy's PD profile is comparable to approved epinephrine injection products.
- neffy has the potential to be an additional option for the first line treatment of (Type I) allergic reactions, including anaphylaxis.







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

Treatment	N	t <sub>max</sub> (min) median (range)	c <sub>max</sub> (pg/mL) mean (%CV)	AUC <sub>last</sub> (min* pg/mL) mean (%CV)	
Single Dosing					
neffy 2.0 mg IN	78	20.5 (2 - 150)	485 (70.6)	40900 (67.5)	
Epinephrine 0.3 mg IM	178	45 (3.9 - 360)	277 (65.4)	27900 (38.7)	
EpiPen 0.3 mg	77	10 (2 - 45)	581 (75.6)	31600 (39.3)	
Epinephrine 0.5 mg IM	123	45 (4 - 360)	399 (65.5)	43700 (34)	
Twice Dosing					
neffy 2.0 mg IN (L/R)	39	30 (6 - 150)	1000 (93.1)	8600 (77)	
neffy 2.0 mg IN (R/R)	39	30 (4 - 150)	922 (75.3)	86500 (60.5)	
Epinephrine 0.3 mg IM (L/R)	70	45 (6 - 180)	436 (48.8)	47500 (32.6)	
EpiPen 0.3 mg (L/R)	78	20 (4 - 360)	754 (64.7)	55000 (47.9)	

**Table 2: Epinephrine Pharmacodynamic Parameters by Treatment** 

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

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