

# PHARMACOKINETICS/PHARMACODYNAMICS AFTER ADMINISTRATION OF ARS-1 (*neffy*<sup>®</sup> NASAL SPRAY), EPINEPHRINE AUTO-INJECTOR, AND MANUAL INTRAMUSCULAR INJECTION

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## RATIONALE

Epinephrine is considered the first-line treatment for severe allergic reactions and anaphylaxis. Epinephrine auto-injectors (EAI) are the most frequently used products for out-of-hospital treatment; however, they are considered inconvenient and cumbersome.

Up to 83% of patients/caregivers reporting failing to administer or delaying use of EAIs, even during a severe allergic reaction.<sup>1</sup> Additionally, 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.<sup>2</sup>

Delayed treatment, defined as treatment after presentation to the emergency department, is associated with a significantly increased risk of hospitalization (odds ratio 4.0 [95% CI, 0.12-0.49]).<sup>3</sup>

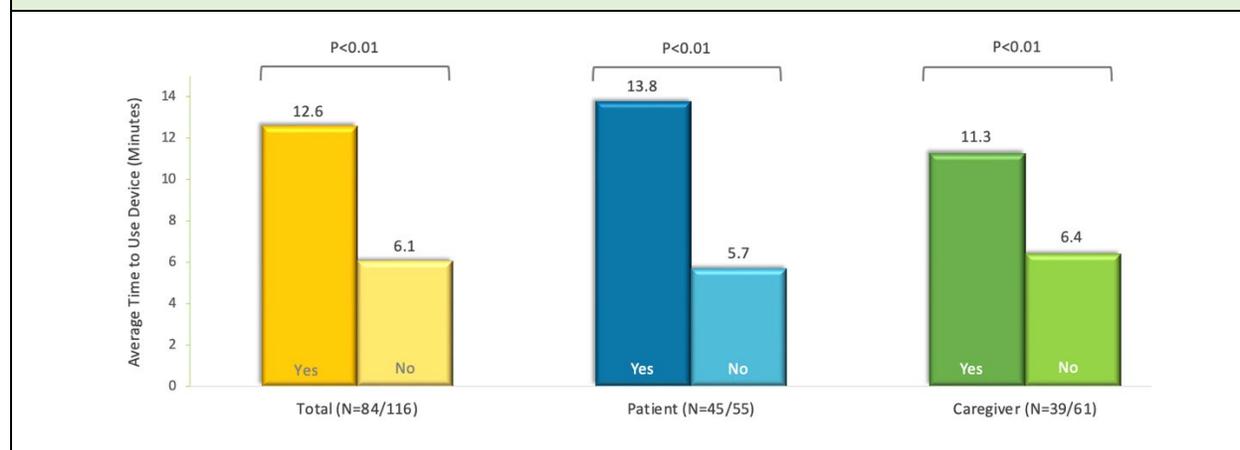
A survey of 200 epinephrine users (100 patients and 100 caregivers) demonstrated that the mean time to dose was significantly higher in patients and caregivers who self-reported delaying treatment or were hesitant to treat (12.6 minutes vs 6.1 minutes,  $p < 0.01$ ) (Figure 1).

There were several factors that were significantly associated with delayed dosing, including the requirement to go to ER, uncertainty about the symptom being warranted for injection, potential side effects, fear to use ( $p < 0.01$ ), pain, and size of device ( $p < 0.05$ ) (Figure 2). These results suggest that an alternative device may decrease hesitancy among patients and caregivers and reduce the time to dose.

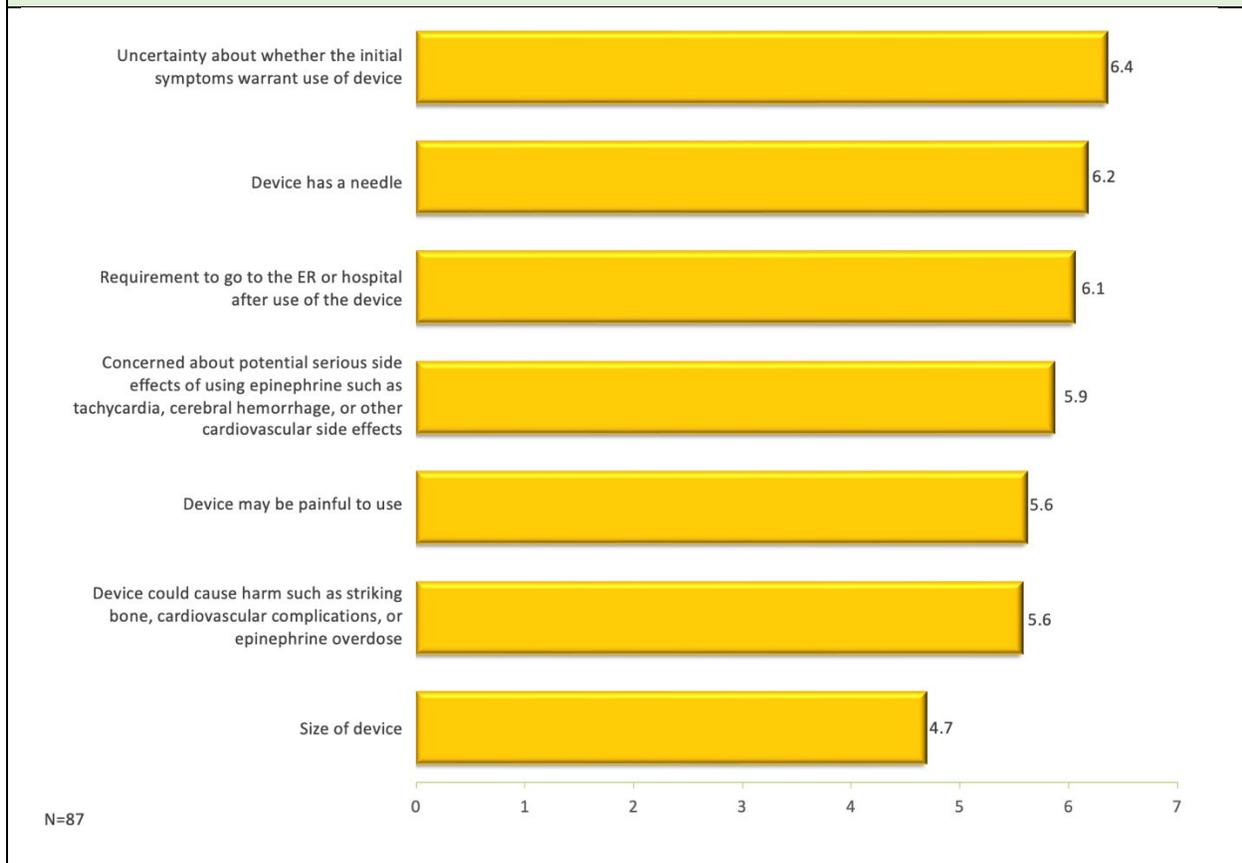
ARS Pharmaceuticals, Inc is developing *neffy*, an intranasal (IN) epinephrine spray that is a needle-free alternative epinephrine delivery device for the emergency treatment of (Type I) allergic reactions, including anaphylaxis.

*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. *neffy* is anticipated to have pharmacokinetic, pharmacodynamic, and safety profiles that are within the range of currently approved epinephrine injection products.

Figure 1: Time to Use by Hesitation and Delay (Yes/No)



**Figure 2: Reason for Delay or Hesitation Using Device with Statistical Difference (P<0.01 or P<0.05)**



## METHODS

EPI 15 was one of a series of studies conducted to evaluate the pharmacokinetics and pharmacodynamics of *neffy*. This pivotal study was a Phase 1, six-treatment, six-period, crossover study in 59 healthy subjects. Each subject received:

- a single dose of *neffy* 2.0 mg IN
- a single dose of EpiPen® 0.3 mg
- ▲ a single dose of Epinephrine manual 0.3 mg Intramuscular Injection (IM)

Pharmacokinetics (mean epinephrine concentrations and epinephrine pharmacokinetic parameters) and pharmacodynamics (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate [HR]) were evaluated for each treatment.

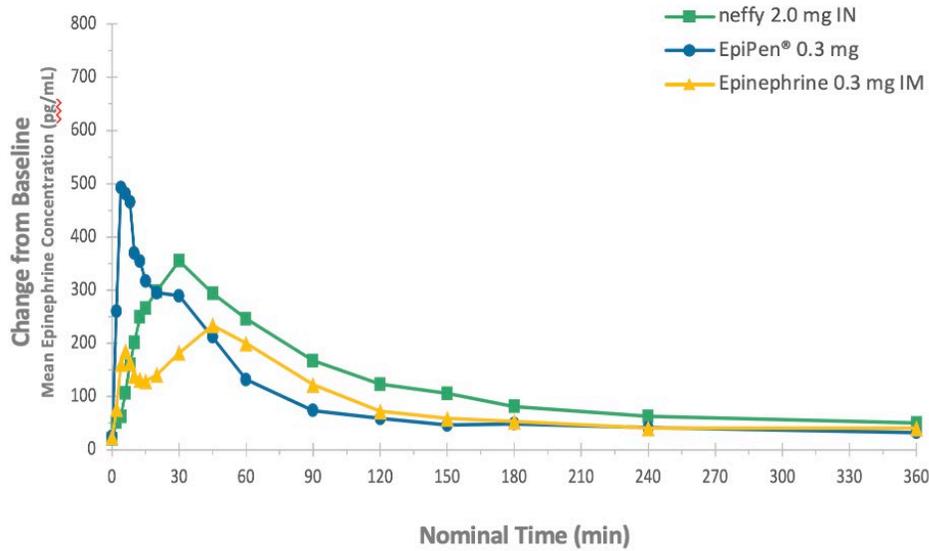
## RESULTS

### Pharmacokinetic Results

Mean epinephrine concentrations were highest for EpiPen until approximately 20 minutes post-dose. From 30 minutes to 360 minutes post-dose, *neffy* exhibited higher mean concentrations compared to EpiPen and Epinephrine IM.

Mean  $C_{max}$  values were highest after EpiPen (753 pg/mL), followed by *neffy* (481 pg/mL), and Epinephrine IM (339 pg/mL). The greatest total exposure was observed after *neffy* (43500 min\*pg/mL), followed by EpiPen (31300 min\*pg/mL), and Epinephrine IM (29300 min\*pg/mL). Median  $t_{max}$  values were fastest following EpiPen (7.50 minutes), followed by *neffy* (30.0 minutes), and Epinephrine IM (45.0 minutes) (Figure 3 and Table 1).

**Figure 3: Change from Baseline - Mean Epinephrine Concentration vs. Time Profiles**



**Table 1: Summary Statistics of Epinephrine Pharmacokinetic Parameters**

Treatment	N	$t_{max}$ (min) median (range)	$C_{max}$ (pg/mL) mean (%CV)	$AUC_{last}$ (min*pg/mL) mean (%CV)
<b>Single Dose</b>				
neffy 2.0 mg IN	42	30.0 (6.00 – 150)	481 (76.0)	43500 (69.4)
EpiPen 0.3 mg	42	7.50 (2.00 – 45.0)	753 (65.6)	31300 (35.0)
Epinephrine 0.3 mg IM	42	45.0 (4.00 – 90.0)	339 (74.1)	29300 (41.7)

$C_{max}$  = maximum plasma concentration;  $T_{max}$  = time to maximum plasma concentration,  $AUC_{last}$  = area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation

**Pharmacodynamic Results**

**Systolic Blood Pressure (Figure 4 and Table 2)**

All treatments resulted in an increase from baseline SBP, with the greatest increase observed following neffy. EpiPen resulted in a smaller and more abrupt increase relative to neffy and only a minimum increase was observed after Epinephrine IM. Mean SBP  $E_{max}$  was higher following neffy relative to both EpiPen and Epinephrine IM.

**Diastolic Blood Pressure (Figure 4 and Table 2)**

neffy resulted in an initial increase from baseline DBP, followed by a decrease from baseline. Both EpiPen and Epinephrine IM resulted in an immediate decrease from baseline DBP.

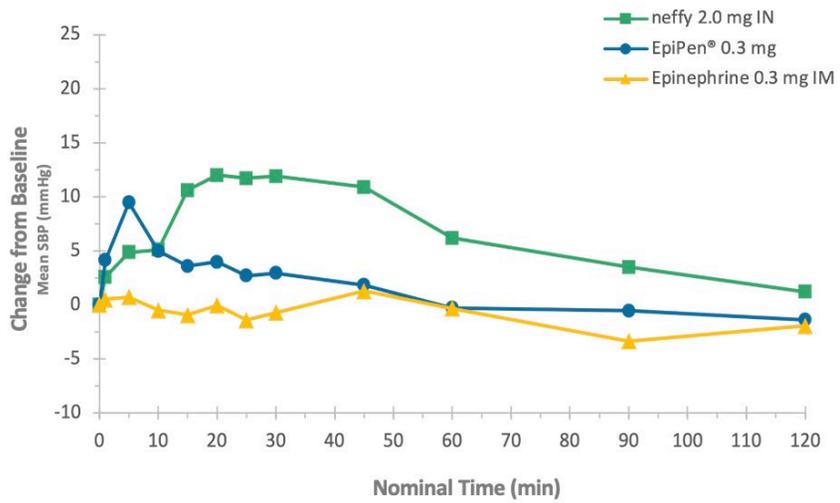
The decrease from baseline was markedly more pronounced following EpiPen and Epinephrine IM relative to neffy. Mean DBP  $E_{max}$  was significantly different following neffy relative to Epinephrine IM and EpiPen.

**Heart Rate (Figure 4 and Table 2)**

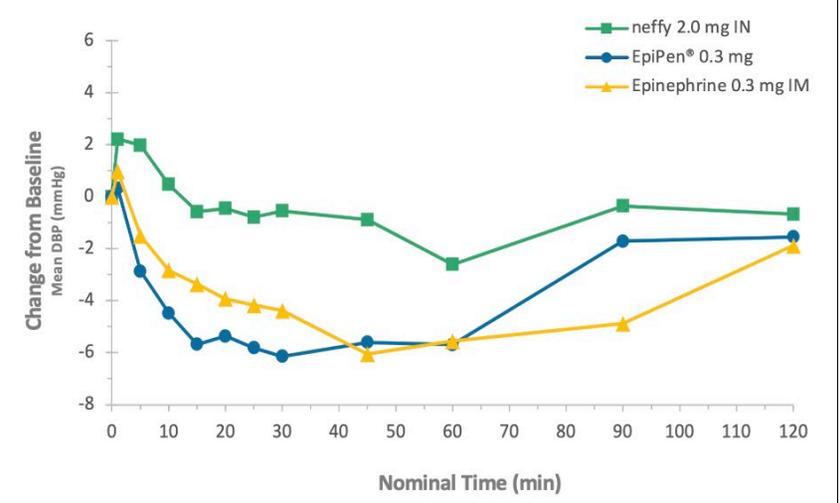
All treatments resulted in increases from baseline HR. There was a return towards baseline after both Epinephrine IM and EpiPen, while the elevation persisted throughout the 120 minutes following neffy. In general,  $E_{max}$  was significantly higher following neffy relative to EpiPen and Epinephrine IM.

**Figure 4: Mean Change from Baseline Pharmacodynamics vs. Time Profiles**

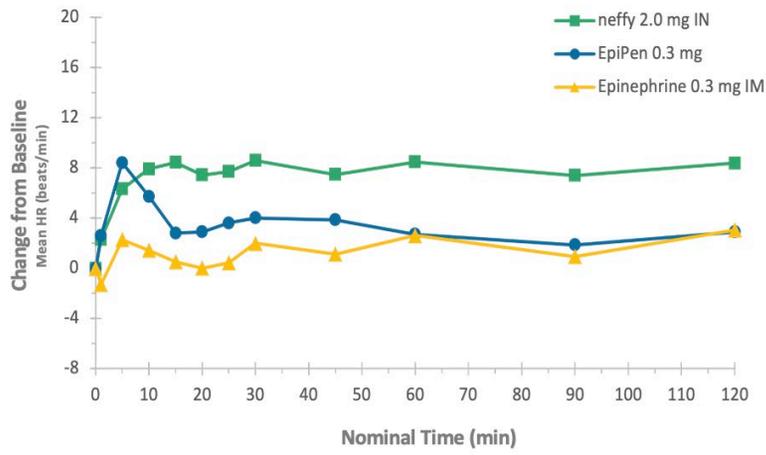
**Systolic Blood Pressure (SBP)**



**Diastolic Blood Pressure (DBP)**



**Heart Rate (HR)**



**Table 2: Maximum Pharmacodynamic Effect (Change from Baseline) and Time to Maximum Pharmacodynamic Effect**

Treatment	N	Mean E <sub>max</sub> (CV)			Median T <sub>max</sub> (min)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP	DBP	HR
<b>Single Dose</b>							
<b>neffy 2.0 mg IN</b>	42	23.6 (64.8)	8.10 (64.3)	17.3 (62.7)	25.0 (1.00 – 116)	13.0 (1.00 – 117)	19.0 (1.00 – 116)
<b>EpiPen 0.3 mg</b>	42	18.2 (80.3)	5.62 (131)	12.3 (63.2)	9.0 (1.00 – 116)	10.0 (1.00 – 115)	10.0 (1.00 – 115)
<b>Epinephrine 0.3 mg IM</b>	42	11.9 (81.0)	5.48 (145)	9.71 (87.1)	22.5 (1.00 – 116)	9.00 (1.00 – 115)	27.0 (1.00 – 117)

E<sub>max</sub> = maximum effect; TE<sub>max</sub> = time to maximum effect;  
SBP = systolic blood pressure; DBP = diastolic blood pressure; PR = pulse rate

### Safety Results

The study treatments were well tolerated, and all treatment emergent adverse events were considered mild. The maximum increase in SBP was 90 mmHg, which was within the range of the currently approved products.

### CONSLUSIONS

*neffy* 2.0 mg IN has a pharmacokinetic profile that is within the range of currently approved injection products (Epinephrine 0.3 mg IM and EpiPen 0.3 mg).

The *neffy* 2.0 mg IN Pharmacodynamic profile is comparable to EpiPen 0.3 mg and is comparable to or better than Epinephrine 0.3 mg IM, suggesting that *neffy* is expected to be at least as efficacious as EpiPen.

Despite having a lower C<sub>max</sub> relative to EpiPen, *neffy* resulted in more pronounced increases in SBP, DBP, and PR. One of the mechanisms by which this occurs likely involves *neffy*'s ability to bypass the powerful β<sub>2</sub>-mediated vasodilation in the skeletal muscle.<sup>4</sup> In contrast to intranasal administration, intramuscular injection in the thigh directly exposes skeletal muscle to the full dose of epinephrine, resulting in the activation of the β<sub>2</sub> receptors that are abundant in the skeletal muscle. This β<sub>2</sub> activation results in vasodilation and a subsequent decrease in peripheral vascular resistance, ultimately resulting in a rapid decrease in DBP.<sup>5</sup>

The pharmacokinetic and pharmacodynamic results of this study demonstrate that *neffy* has

the potential to be a safe, effective, and more convenient alternative for the emergency treatment of (Type I) allergic reactions, including anaphylaxis or what's commonly referred to as severe allergic reactions.

In addition to being a safe and effective alternative to injections, *neffy* is anticipated to have significant clinical benefit by providing patients and caregivers with an easier-to-use, needle-free device that eliminates the fear and uncertainty associated with injectable products.

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*Presented at the Eastern Food Allergy and Comorbidity Conference; January 5, 2023; Palm Beach, FL*