

# A Single-Period, Single-Dose Study of the Pharmacokinetics of Epinephrine After Administration of Intranasal ARS-1 (*neffy*<sup>®</sup> Nasal Spray) to Pediatric Subjects with a History of Systemic Allergic Reactions

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## RATIONALE

The current global prevalence of pediatric anaphylaxis is estimated to be as high as 1.8%<sup>1</sup>, with food allergies being the most frequent trigger.<sup>1</sup> There has been a significant rise in the prevalence of food allergies over the past several decades<sup>2</sup>, and approximately 40% of children with food allergies have experienced a severe allergic reaction such as anaphylaxis.<sup>3</sup>

Epinephrine is considered the first-line treatment for severe allergic reactions and anaphylaxis<sup>4,5,6</sup>, and epinephrine auto-injectors (EAI) are the most frequently used products for out-of-hospital treatment; however, they are considered inconvenient, cumbersome and painful to administer with up to 83% of patients/caregivers reporting failing or delaying use of EAI, even during a severe allergic reaction.<sup>7</sup>

*neffy* is an intranasal (IN) epinephrine spray and needle-free delivery device being developed as an alternative to EAI 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.

A series of well-controlled clinical trials in adult subjects has demonstrated that *neffy* results in consistent pharmacokinetic (PK) and pharmacodynamic (PD) responses. The present study was conducted to evaluate the PK and PD of *neffy* in pediatric allergy subjects ranging from 4 to 17 years of age.

## METHOD

This was a Phase 1, single-dose, single-treatment study in pediatric allergy subjects. Each subject received one dose of *neffy* based on body weight:

- A single dose of *neffy* 0.65 mg (subjects between 15 kg and 30 kg)
- A single dose of *neffy* 1.0 mg (Subjects >30 kg) OR
- ▲ A single dose of *neffy* 2.0 mg (Subjects >30 kg)

Pharmacokinetic, pharmacodynamic, and safety variables were assessed.

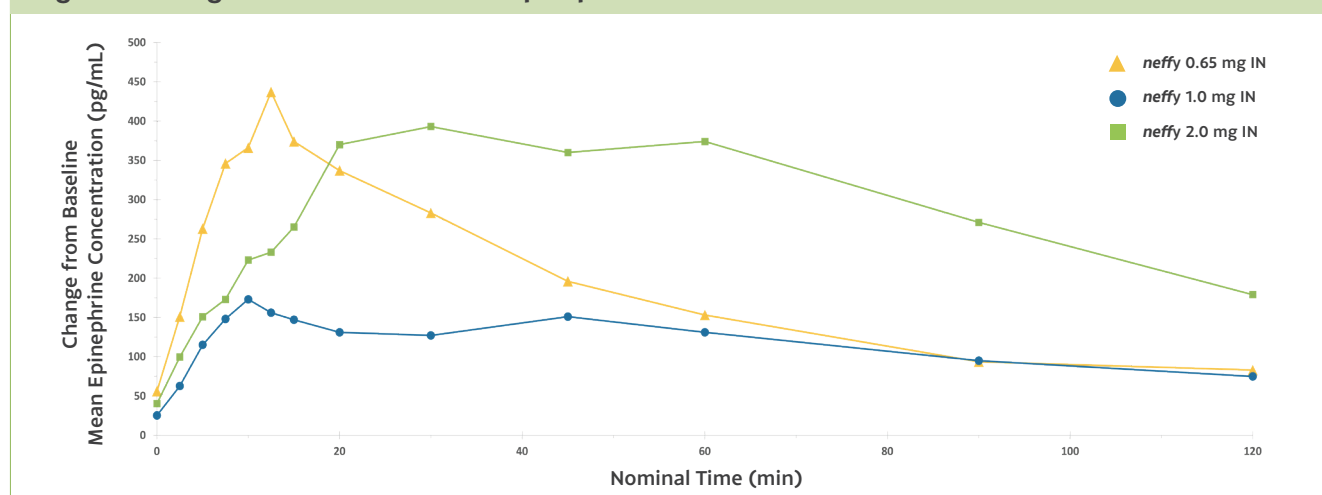
## RESULTS: PHARMACOKINETIC

Mean concentration-time curves are presented in Figure 1.

In pediatric subjects >30 kg, 1.0 mg and 2.0 mg doses of *neffy* resulted in mean  $C_{max}$  values of 253 pg/mL and 540 pg/mL, respectively. The results are comparable to or slightly higher than the results observed in adult subjects (276 pg/mL and 485 pg/mL for 1 mg and 2 mg doses, respectively). (Table 1)

In pediatric subjects between 15kg and 30 kg, *neffy* 0.65 mg resulted in a mean  $C_{max}$  of 534 pg/mL. (Table 1)

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



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

Treatment	N	$t_{max}$ (min) median (range)	$c_{max}$ (pg/mL) mean (%CV)	AUC <sub>last</sub> (min* pg/mL) mean (%CV)
<b>15 kg to 30 kg</b>				
<i>neffy</i> 0.65 mg IN	11	12.5 (2.50 - 30.0)	534 (58.7)	21900 (49.7)
<b>&gt; 30 kg</b>				
<i>neffy</i> 1.0 mg IN	25	20.0 (7.50 - 120)	253 (66.2)	14000 (53.0)
<i>neffy</i> 2.0 mg IN	16	25.0 (2.50 - 120)	540 (70.7)	35500 (76.3)

**RESULTS: PHARMACODYNAMIC**

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

In pediatric subjects >30 kg, 1.0 mg and 2.0 mg doses of *neffy* resulted in a mean maximum response (SBP)  $E_{max}$  of 8.23 mmHg and 11.9 mmHg, respectively. In pediatric subjects between 15 kg and 30 kg, *neffy* 0.65 mg resulted in a mean SBP  $E_{max}$  of 12.25 mmHg.

**Diastolic Blood Pressure (Table 2 and Figure 3)**

In pediatric subjects >30 kg, 1.0 mg and 2.0 mg doses of *neffy* resulted in a mean DBP  $E_{max}$  of 4.92 mmHg and 7 mmHg, respectively. In pediatric subjects between 15 kg and 30 kg, *neffy* 0.65 mg resulted in a mean DBP  $E_{max}$  of 10.6 mmHg.

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

In pediatric subjects >30 kg, 1 mg and 2 mg doses of *neffy* resulted in a mean HR  $E_{max}$  of 13.8 bpm and 15.4 bpm, respectively. In pediatric subjects between 15 kg and 30 kg, *neffy* 0.65 mg resulted in a mean HR  $E_{max}$  of 17.7 bpm.

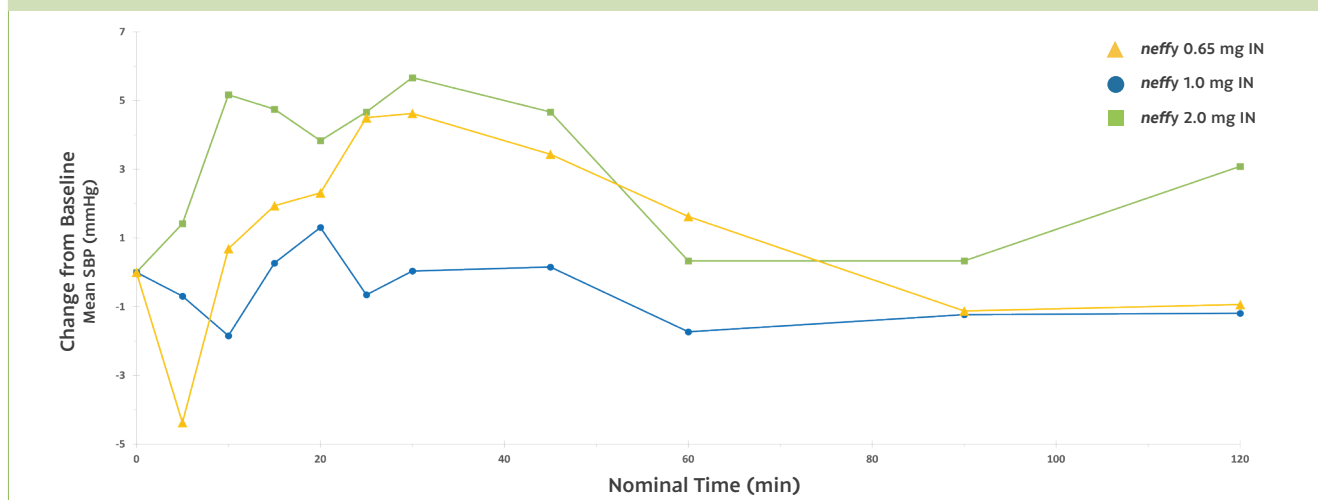
**Safety Results**

*neffy* demonstrated a positive safety profile. There was one moderate TEAE (nasal discomfort following administration of *neffy* 2.0 mg in a subject > 30 kg). All other TEAEs were considered mild.

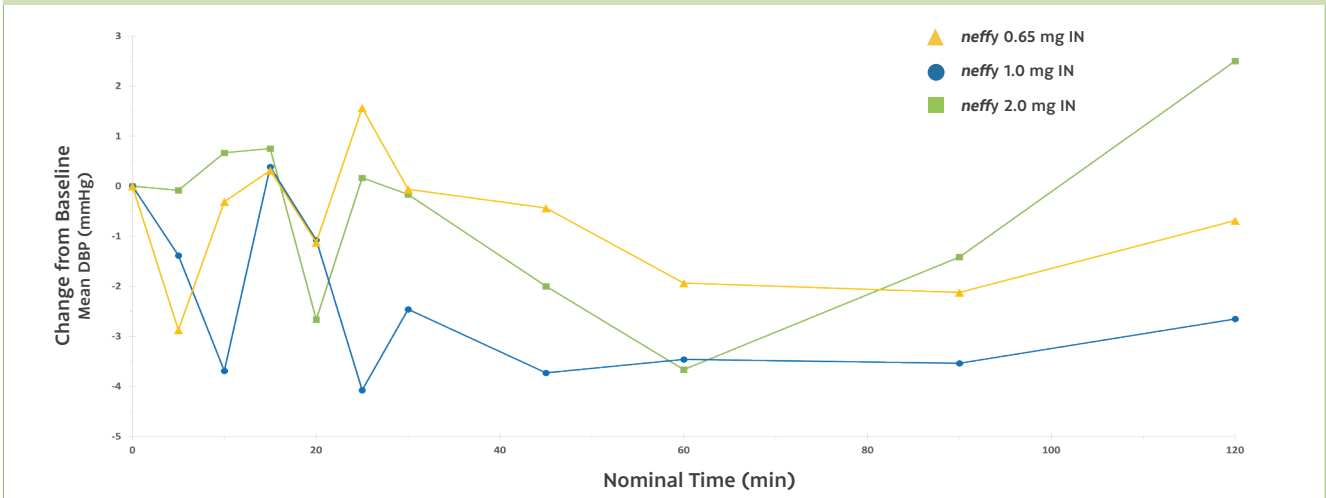
**CONCLUSION**

In pediatric allergy subjects, both the 1.0 mg and 2.0 mg doses of *neffy* result in pharmacokinetics that are comparable to what has been observed in adults.

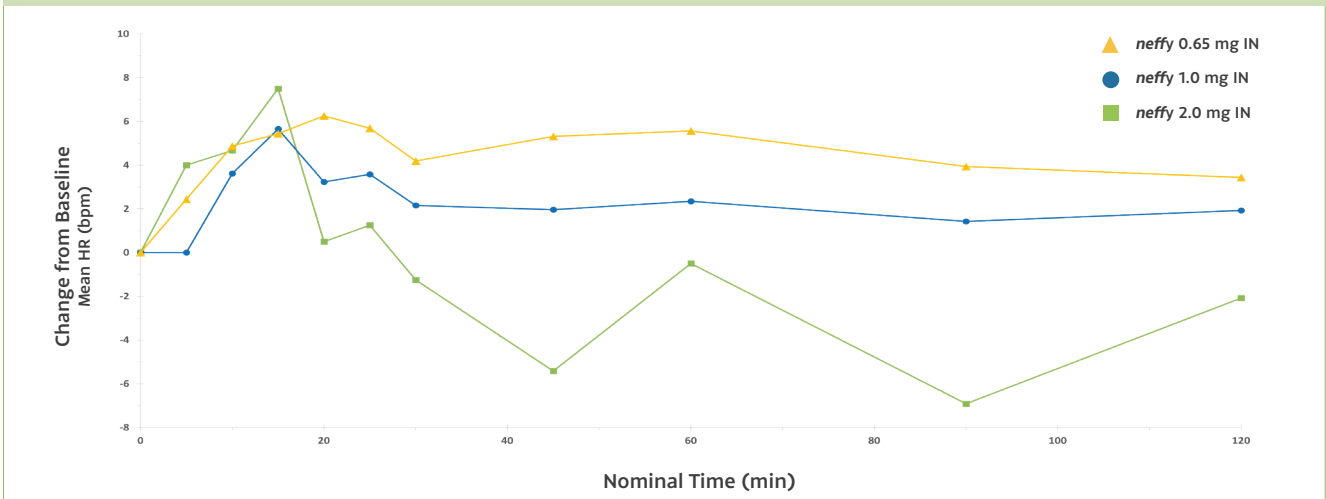
**Figure 2: Change from Baseline - Mean Systolic Blood Pressure (SBP) versus Time Profiles by Treatment**



**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**



**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>E<sub>max</sub></sub> (min)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP	DBP	HR
<b>15 kg to 30 kg</b>							
neffy 0.65 mg IN	11	12.25 (43.5)	10.6 (80.3)	17.7 (83.8)	30.5 (10-120)	25 (0-120)	10.5 (0-91)
<b>&gt; 30 kg</b>							
neffy 1.0 mg IN	25	8.23 (85.3)	4.92 (91.2)	13.8 (72.4)	20 (0-120)	15.5 (0-122)	18 (0-124)
neffy 2.0 mg IN	16	11.9 (68.6)	7 (76.0)	15.4 (75.0)	25 (0-90)	17.5 (0-120)	32.5 (0-90)

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