Pharmacokinetics of Self-Administration of ARS-1 (*neffy*® Nasal Spray) 2.0 mg Versus Manual Intramuscular (IM) Epinephrine 0.3 mg by Health Care Provider (HCP)

Poster Number: 9

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RATIONALE

Epinephrine is considered the first-line treatment for severe allergic reactions and anaphylaxis[1,2,3], and epinephrine auto-injectors (EAIs) are the most frequently used products for out-of-hospital treatment.

The effective treatment of severe allergic reactions and anaphylaxis in an out-of-hospital setting requires that patients and caregivers be willing and able to correctly administer epinephrine in a timely manner; however, EAIs are considered inconvenient and cumbersome, with up to 83% of patients/caregivers reporting failure to administer or delaying the use of EAIs, even when they know they are having a severe allergic reaction.[4,5,6,7]

neffy is an intranasal (IN) epinephrine spray that is a needle-free delivery device being developed as an alternative to EAIs 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 study was conducted to evaluate and compare the pharmacokinetics and pharmacodynamics of self-administered ***neffy*** 2.0 mg relative to staff-administered manual intramuscular epinephrine 0.3 mg injection by needle and syringe in allergy subjects.

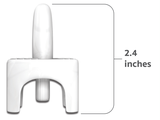
METHODS

Phase 1, single-dose, two-treatment, two-period, randomized crossover study in subjects with a history of allergic rhinitis. Each subject was randomized to receive:

- A single 2.0 mg/100 µL IN dose of ***neffy*** (Figure 1) self-administered into one nostril; OR
- A single 0.3 mg IM epinephrine injection (0.3 mL) study staff-administered in the anterolateral thigh of the right leg.
- Subjects were crossed over to receive the other treatment after a 24 hour washout period.

Self-administration training for ***neffy*** was conducted during screening, but no other instructions were provided until dosing. At dosing, the Quick Reference Guide included with the ***neffy*** secondary packaging was provided with ***neffy*** to mimic real-life situations where training may have not been provided.

Figure 1: Single 2.0 mg/100 µL IN Dose of *neffy*



RESULTS

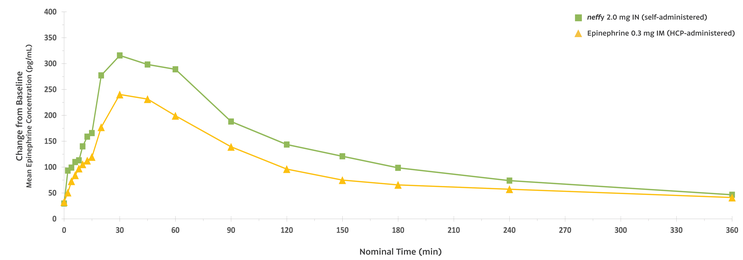
DOSING ERRORS FOLLOWING *neffy* SELF-ADMINISTRATION

- Forty-two of 42 subjects (100%) were able to successfully remove the ***neffy*** nasal spray device from the blister packaging. No subjects (0/42, 0%) refused to dose with ***neffy***. No subjects (0/42, 0%) made an error dosing the nasal sprayer that resulted in no dose being administered. No subjects (0/42, 0%) failed to properly press the plunger enough to activate the spray.
- The average dosing time for ***neffy*** was 18.47 seconds.

PHARMACOKINETIC RESULTS

- Overall, ***neffy*** resulted in higher epinephrine exposures relative to Epinephrine 0.3 mg IM. (Figure 2)

Figure 2: Change from Baseline - Mean Epinephrine Concentration versus Time Profiles



PHARMACOKINETIC RESULTS (Continued)

- ***neffy*** resulted in a mean peak exposure (C_{max}) of 421 pg/mL and Epinephrine 0.3 mg IM resulted in a mean peak exposure of 322 pg/mL (p = 0.1333, 95% CI 97.86 – 158.27). ***neffy*** resulted in a median time to maximum concentration (t_{max}) of 30.0 minutes. Epinephrine 0.3 mg IM resulted in median time to maximum concentration of 45.0 minutes. Mean overall exposure (AUC_{last}) was 46776 min*pg/mL following ***neffy*** and 33494 min*pg/mL following Epinephrine 0.3 mg IM (p = 0.0318, 95% CI 106.07 – 152.93). (Table 1)

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)
neffy 2.0 mg IN	42	30.0 (6.0 - 240)	421 (66.4)	46776 (55.9)
Epinephrine 0.3 mg IM	42	45.0 (4.0 - 120)	322 (65.0)	33494 (41.0)

PHARMACODYNAMIC RESULTS

Systolic Blood Pressure (SBP) (Table 2 and Figure 3)

- ***neffy*** resulted in an increase from baseline SBP that persisted throughout the entire 120-minute sampling period. Epinephrine 0.3 mg IM resulted in an initial increase from baseline SBP that persisted for approximately 10-minutes post-dose, at which point SBP returned to baseline and, eventually, to below baseline.
- ***neffy*** resulted in a mean peak effect of (SBP E_{max}) of 20 mmHg, and Epinephrine 0.3 mg IM resulted in a mean peak effect of 13 mmHg (p<0.0001, 95% CI 4.55 – 10.06).
- ***neffy*** resulted in a median time to maximum effect (T_{Emax}) of 18 minutes and Epinephrine 0.3 mg IM resulted in a median time to maximum effect of 16 minutes.

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

- Both treatments resulted in an initial increase from baseline DBP, with ***neffy*** resulting in a more pronounced increase. By the 10-minute timepoint, both treatments resulted in a return to baseline, however Epinephrine 0.3 mg IM resulted in a markedly greater decrease from baseline that persisted throughout the 120-minute sampling period.
- ***neffy*** resulted in a mean peak effect of (DBP E_{max}) of 9 mmHg, and Epinephrine 0.3 mg IM resulted in a mean peak effect of 8 mmHg (p = 0.1961, 95% CI -0.37 – 2.96).
- Both treatments resulted in a median time to maximum effect (T_{Emax}) of 5 minutes.

Heart Rate (HR) (Table 2 and Figure 5)

- Both treatments resulted in an initial increase from baseline HR. This increase persisted throughout the entire sampling period following ***neffy***, however following Epinephrine 0.3 mg IM, HR returned to near-baseline levels by approximately 15-minutes post-dose.
- ***neffy*** resulted in a mean peak effect (HR E_{max}) of 13 bpm, and Epinephrine 0.3 mg IM resulted in a mean peak effect of 10 bpm (p = 0.1102, 95% CI -0.07 – 4.88).
- ***neffy*** resulted in a median time to maximum effect (T_{Emax}) of 18 minutes and Epinephrine 0.3 mg IM resulted in a median time to maximum effect of 13 minutes.

SAFETY RESULTS

neffy demonstrated an overall safety profile, including an adverse event profile, that was similar to Epinephrine 0.3 mg IM.

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

Treatment	N	Mean E_{max} (CV)			Median T_{Emax} (min)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP	DBP	HR
neffy 2.0 mg IN	42	20 (47.4)	9 (56.6)	13 (59.3)	18 (1-117)	5 (1-117)	18 (1-117)
Epinephrine 0.3 mg IM	42	13 (60.2)	8 (71.8)	10 (69.1)	16 (1-117)	5 (1-117)	13 (1-117)

Figure 3: Change from Baseline - Mean SBP versus Time Profiles

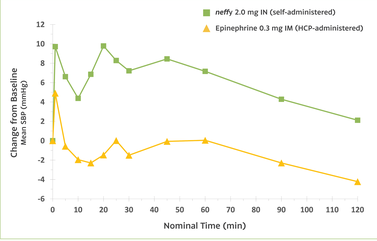


Figure 4: Change from Baseline - Mean DBP versus Time Profiles

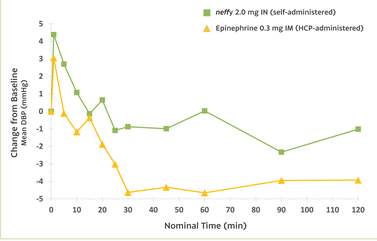
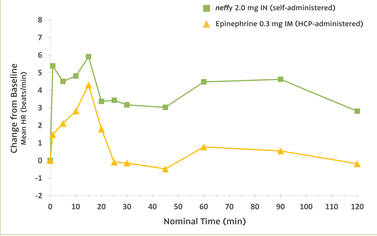


Figure 5: Change from Baseline - Mean HR versus Time Profiles



DISCUSSION

- Under circumstances designed to mimic real-world use, all 42 subjects were able to successfully dose ***neffy***.
- After self-administration, ***neffy*** resulted in greater peak exposures (C_{max}) and in more rapid time to peak exposures (t_{max}) relative to Epinephrine 0.3 mg IM. ***neffy*** also resulted in greater overall exposures (AUC_{0-t}) relative to Epinephrine 0.3 mg IM.
- ***neffy*** resulted in more pronounced and persistent increases in SBP, DBP, and HR relative to Epinephrine 0.3 mg IM. By approximately 10-minutes post-dose, a decrease in DBP was observed for both treatments, however this decrease was less pronounced following ***neffy***.

CONCLUSION

neffy resulted in greater overall pharmacokinetic exposure relative to Epinephrine 0.3 mg IM, with more pronounced increases in SBP, DBP, and HR. These findings are consistent with previous ARS studies using ***neffy*** vs Epinephrine 0.3 mg IM. Additionally, ***neffy***'s PK and PD profiles in this self-administration study are consistent with earlier studies in which ***neffy*** was administered by trained medical professionals. Taken together, these results demonstrate that ***neffy*** is a safe and easy-to-use additional option for epinephrine delivery and is expected to be efficacious for the treatment of severe allergic reactions and anaphylaxis.

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Presented at the American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting: February 24, 2023; San Antonio, TX