Pharmacokinetics/Pharmacodynamics After Administration of ARS-1 (*neffy*® Nasal Spray), Epinephrine Auto-Injector, and Manual Intramuscular Injection

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RATIONALE

Epinephrine auto-injectors (EAIs) are the most frequently used products for out-of-hospital treatment for severe allergic reactions and anaphylaxis; however, they are considered inconvenient, cumbersome and painful to administer with up to 83% of patients/caregivers reporting failing or delaying use of EAIs, even during a severe allergic reaction.[1]

ARS Pharmaceuticals, Inc is developing *neffy*, an intranasal (IN) epinephrine spray that is anticipated to have pharmacokinetic, pharmacodynamic, and safety profiles that are within the range of currently approved epinephrine injection products.

METHODS

EPI 15 was one of a series of studies conducted to evaluate the pharmacokinetics and pharmacodynamics of *neffy*. This pivotal study was 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 0.3 mg manual 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 (Figure 1 and Table 1)

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 injection (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).

PHARMACODYNAMIC RESULTS

Systolic Blood Pressure (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 (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 (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.

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.

CONCLUSION

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* 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.

After decades of epinephrine treatments limited to delivery by injections, ARS-1 (*neffy*® Nasal Spray) is embarking on the next generation of rescue therapy using an intranasal system that delivers a consistent pharmacokinetic exposure of epinephrine when compared to existing treatments. By removing hesitation caused by fear of needles, *neffy*® Nasal Spray may improve patient and caregiver preparedness and response time when epinephrine medication is needed, allowing it to be used quickly and confidently at the first sign of a life-threatening allergic reaction.

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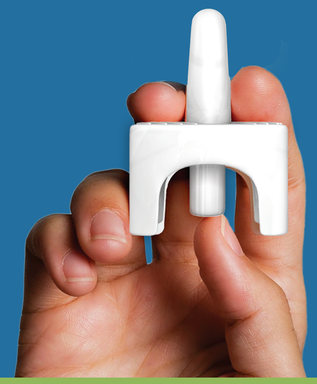

Figure 1: Change from Baseline - Mean Epinephrine Concentration versus Time Profiles

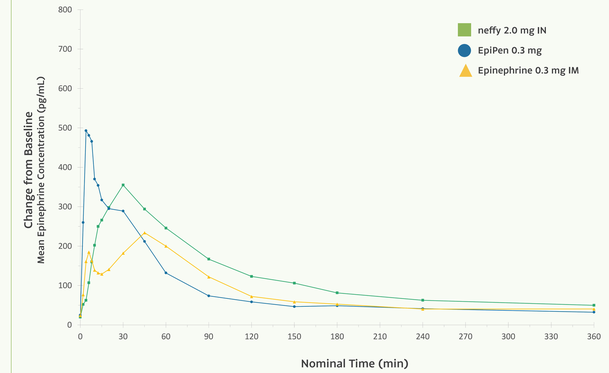

Table 1: Summary Statistics of Epinephrine Pharmacokinetic Parameters

Treatment	N	t_{max} (min) median (range)	C_{max} (pg/mL) mean (%CV)	AUC_{last} (min* pg/mL) mean (%CV)
Single Dose				
***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)

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

Treatment	N	Mean E_{max} (CV) median (range)			Median T_{max} (min) mean (%CV)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP	DBP	HR
Single Dose							
***neffy* 2.0 mg IN**	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)
EpiPen 0.3 mg	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)
Epinephrine 0.3 mg IM	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)

REFERENCES

1. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J, Hyer W, Vance G, Townshend C, Alfaham M, Arkwright PD, Rao R, Kapoor S, Summerfield A, Warner JO, Roberts G. The use of adrenaline autoinjectors by children and teenagers. Clin Exp Allergy. 2012 Feb;42(2):284-92.

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