The Pharmacokinetic and Pharmacodynamic Properties of Intranasal Epinephrine Spray (*neffy*) Compared to Manual Intramuscular Administration, EpiPen, and Symjepi: an Integrated Analysis

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RATIONALE

- Clinically, epinephrine appears to work rapidly following systemic administration, regardless of the route of administration or device. However, administration via intravenous bolus may result in overdose, rapid cardiovascular changes, and inaccurate dilution[1-3]
- The labels of approved epinephrine products have similar "indication and usage," "dosage and administration," "warning and precaution," and "adverse reactions." The guidelines for the treatment of anaphylaxis do not differ based on the type of epinephrine product being used
- Although recent studies have demonstrated that there are pharmacokinetic (PK) differences among EpiPen/other auto-injectors and manual intramuscular (IM) injection,[4,5] the corresponding differences in pharmacodynamic (PD) parameters have not been assessed
- A novel intranasal (IN) epinephrine spray (*neffy*; ARS Pharmaceuticals, Inc.) is being developed as a potential alternative to IM epinephrine administration. PK and PD parameters of this novel route of administration are being explored

METHODS

- An integrated PK analysis was conducted across 4 randomized crossover clinical trials to compare the PK and PD parameters of *neffy* 1 mg administered as a nasal spray and 0.3-mg doses of EpiPen, Symjepi, and IM epinephrine administered manually (epinephrine 0.3 mg)
- A total of 175 participants were included in the analysis. Studies included in this analysis were phase 1, open-label, randomized, single-dose crossover studies. A summary of the individual studies is presented in **Table 1**

Table 1. Summary of Individual Studies Included in the Integrated Pharmacokinetic Analysis

Study	Treatments Included in the Analysis	Subjects
Study 1	*neffy* 1 mg IN Epinephrine 0.3 mg IM	70 healthy volunteers aged 21-55 years
Study 2	*neffy* 1 mg IN Epinephrine 0.3 mg IM	36 healthy volunteers aged 19-55 years
Study 3	*neffy* 1 mg IN EpiPen 0.3 mg	36 healthy volunteers aged 19-54 years
Study 4	*neffy* 1 mg IN EpiPen 0.3 mg Symjepi 0.3 mg	36 patients with type I allergies aged 21-54 years

IM, intramuscular; IN, intranasal.

RESULTS

C_{max} Values After Administration

- The epinephrine concentration-versus-time curve indicated that the highest mean concentration occurred after administration via EpiPen, followed by Symjepi, epinephrine 0.3 mg IM, and *neffy* (**Figure 1**)
- The highest geometric mean maximum concentration (C_{max}) values were observed following EpiPen (393 pg/mL) and Symjepi (359 pg/mL)
- The geometric mean C_{max} of *neffy* (204 pg/mL) was comparable to manual epinephrine 0.3 mg IM (217 pg/mL) (**Table 2; Figure 1**)

T_{max} Values After Administration

- The longest median time to maximum concentration (T_{max}) occurred following epinephrine 0.3 mg IM (45 minutes), followed by Symjepi and *neffy* (both 30 minutes) and EpiPen (20 minutes) (**Table 2**)

Systolic Blood Pressure Response

- The greatest mean maximum systolic blood pressure (SBP) change from baseline (E_{max}) was observed following EpiPen (18.1 mmHg). Smaller SBP responses were observed following *neffy,* Symjepi, and epinephrine 0.3 mg IM (16.9, 14.9, and 10.9 mmHg, respectively) (**Table 3; Figure 2**)
- The longest time to reach the maximum SBP response (TE_{max}) was observed following epinephrine 0.3 mg IM (30.5 minutes), followed by *neffy* (21.0 minutes), EpiPen (18.0 minutes), and Symjepi (16.0 minutes)

Diastolic Blood Pressure Response

- The greatest mean maximum diastolic blood pressure (DBP) change from baseline was observed following *neffy* (9.32 mmHg). Smaller DBP responses were observed following epinephrine 0.3 mg IM (5.51 mmHg), Symjepi (5.78 mmHg), and EpiPen (5.93 mmHg) (**Table 3; Figure 2**)
- The longest DBP TE_{max} was observed following EpiPen (25.0 minutes), followed by Symjepi (18.0 minutes), *neffy* (15.0 minutes), and epinephrine 0.3 mg IM (9.0 minutes)

Pulse Rate Response

- The mean maximum pulse rate (PR) change from baseline was similar among *neffy* (13.6 bpm), EpiPen (14.4 bmp), and manual epinephrine 0.3 mg IM (12.8 bpm). Symjepi resulted in a lower maximum PR response (8.86 bpm) (**Table 3; Figure 2**)
- The longest PR TE_{max} was observed following manual epinephrine 0.3 mg IM (30.0 minutes), followed by *neffy* (20.0 minutes), EpiPen (16.0 minutes), and Symjepi (14.0 minutes)

PK/PD Relationship

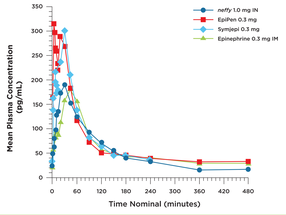
- For both SBP and PR, there is a positive relationship between C_{max} and E_{max}; however, this relationship appears to be limited to lower C_{max} levels. Once C_{max} levels reach approximately 500 pg/mL, additional increases in C_{max} do not translate into increases in E_{max}. This observation was noted across all treatments (**Figures 3 and S1**)
- When the change from baseline SBP is plotted against C_{max}, it appears that *neffy* results in consistent increases in SBP. In contrast, the relationship between change from baseline SBP and C_{max} for both EpiPen and Symjepi appears to be less well defined. While there does appear to be a positive relationship between change from baseline SBP and C_{max} for epinephrine IM, the overall SBP response following *neffy* is far more robust (16.9 vs 10.9 mmHg) (**Table 3; Figure 3**)
- A similar pattern is observed when the change from baseline DBP is plotted against C_{max}. *neffy* is more likely to result in consistent increases in DBP as compared to injection products, particularly at therapeutic C_{max} levels. This observation is consistent with the higher DBP E_{max} of *neffy* (**Table 3; Figure 4**)
- In the SBP and DBP plot from publications, there was a transient decrease in DBP as concentrations increase with intravenous infusion and a gradual return toward baseline as epinephrine levels increased (**Figure 5**). This is likely due to the β_2-mediated vasodilatation that occurs in skeletal muscle at lower epinephrine levels, which is reversed by α_1-mediated vasoconstriction that occurs with higher epinephrine concentrations

Table 2. Comparison of PK Parameters Across Products

Product	N	C_{max} (pg/mL) Geometric Mean (CV%)	AUC_{0-t} (min*pg/mL) Geometric Mean (CV%)	Median T_{max} (minutes) (range)
neffy 1.0 mg IN	135	204 (81.0)	20,100 (65.2)	30.0 (0.0-150)
Epinephrine 0.3 mg IM	104	217 (61.6)	25,600 (34.8)	45.0 (0.0-360)
Symjepi 0.3 mg	36	359 (77.0)	21,800 (50.2)	30.0 (4.0-90.0)
EpiPen 0.3 mg	71	393 (82.6)	25,500 (44.6)	20.0 (3.0-154)

AUC, area under the curve; C_{max}, maximum concentration; CV, coefficient of variation; IM, intramuscular; IN, intranasal; PK, pharmacokinetic; T_{max}, time to maximum concentration.

Figure 1. Mean Plasma Epinephrine Levels Versus Time Following *neffy*, Epinephrine 0.3 mg IM Injection, EpiPen, and Symjepi



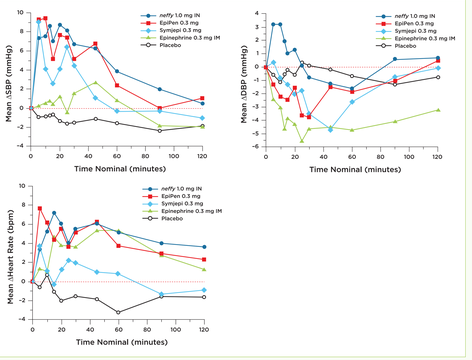
IM, intramuscular; IN, intranasal.

Table 3. E_{max} Parameters by Treatment

Product	N	E_{max} Mean (SD)			TE_{max} Median (Range)		
		SBP (mmHg)	DBP (mmHg)	PR (bpm)	SBP (min)	DBP (min)	PR (min)
neffy IN (1.0 mg)	100	16.9 (10.9)	9.32 (7.46)	13.6 (9.12)	21.0 (0.970-119)	15.0 (0.830-119)	20.0 (2.00-120)
Epinephrine IM (0.3 mg)	68	10.9 (7.29)	5.51 (5.88)	12.8 (7.61)	30.5 (0.970-120)	9.0 (0.970-120)	30.0 (1.97-120)
Symjepi (0.3 mg)	36	14.9 (11.4)	5.78 (6.45)	8.86 (8.53)	16.0 (4.00-115)	18.0 (4.00-115)	14.0 (4.00-115)
EpiPen (0.3 mg)	71	18.1 (10.1)	5.93 (6.23)	14.4 (10.2)	18.0 (4.98-119)	25.0 (4.00-119)	16.0 (5.00-85.0)

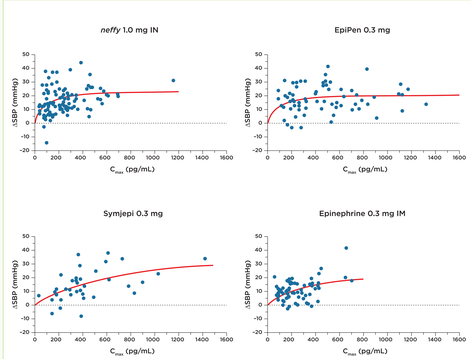
bpm, beats per minute; DBP, diastolic blood pressure; E_{max}, maximum response; IM, intramuscular; IN, intranasal; PR, pulse rate; SBD, systolic blood pressure; SD, standard deviation; TE_{max}, time to reach maximum systolic blood pressure.

Figure 2. SBP, DBP, and HR E_{max}, by Treatment



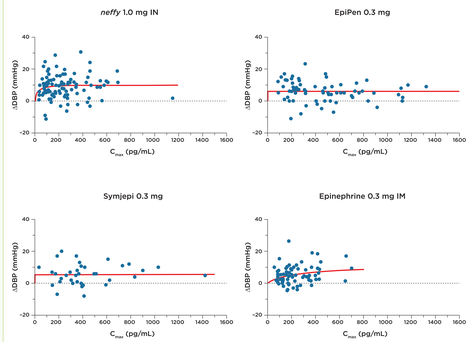
bpm, beats per minute; DBP, diastolic blood pressure; E_{max}, maximum response; HR, heart rate; IM, intramuscular; IN, intranasal; SBD, systolic blood pressure.

Figure 3. SBP E_{max} Versus C_{max}



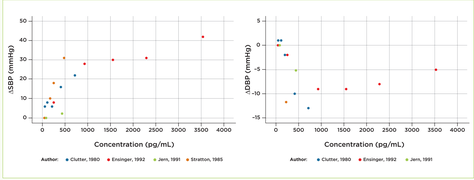
BP, blood pressure; C_{max}, maximum concentration; E_{max}, maximum response; IM, intramuscular; IN, intranasal; SBD, systolic blood pressure.

Figure 4. DBP E_{max} Versus C_{max}



BP, blood pressure; C_{max}, maximum concentration; DBP, diastolic blood pressure; E_{max}, maximum response; IM, intramuscular; IN, intranasal.

Figure 5. SBP and DBP Versus Epinephrine Concentrations Based on Publications



DBP, diastolic blood pressure; SBP, systolic blood pressure.

DISCUSSION

- The differences in the speed of absorption between different injection products do not result in any known differences in clinical efficacy. Nonetheless, there are notable differences in the PK and PD between IM injection and IN administration, as well as among the different injection products
- Even with a lower or comparable mean C_{max} relative to Symjepi and IM injection, *neffy* produced a more robust increase in SBP (SBP E_{max}). This is most likely due to the differential activation of β_2 adrenergic receptors, which mediates vasodilation in the skeletal muscle
- Given that β_2 receptors in the vascular system are predominantly located in skeletal muscle, they are mostly likely to be activated by direct IM injection of epinephrine (either manual injection or via auto-injector), resulting in a greater decrease in DBP. The IN route of administration of *neffy* largely circumvents the β_2 receptor activation in skeletal muscle and may not result in a transient decrease in DBP. By avoiding this initial drop in DBP, the IN route of administration of *neffy* results in a more rapid and greater overall increase in SBP
- There appears to be a ceiling effect for SBP E_{max}, whereby maximum PD expression is achieved at epinephrine levels that are below the highest C_{max} levels. Thus, any additional increases in C_{max} do not result in corresponding increases in SBP. This finding was observed in the present analysis and is supported by published data

CONCLUSIONS

- *neffy* 1 mg IN resulted in C_{max} levels that were similar to those observed following epinephrine 0.3 mg IM and lower than those observed following Symjepi and EpiPen
- Despite having lower C_{max} levels than EpiPen or Symjepi, *neffy* resulted in comparable or higher SBP increases and lower DBP decreases compared with IM injection
- *neffy* may increase SBP more efficiently than injections, as the IN route of administration helps to bypass the β_2 receptor–mediated vasodilation that occurs when epinephrine is injected into skeletal muscle. This is particularly important during the treatment of anaphylaxis, when blood vessels are already dilated in response to the release of histamine

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