

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

S Tanimoto,¹ A Nowak-Wegrzyn,² AK Ellis,³ M Kaliner,⁴ R Lowenthal¹

¹ARS Pharmaceuticals, San Diego, CA, USA; ²NYU Grossman School of Medicine, New York, NY, USA; ³Kingston General Health Research Institute, Kingston, ON, Canada; ⁴Institute for Asthma and Allergy, Chevy Chase, MD, USA

RATIONALE

- Epinephrine is considered the first-line treatment for severe allergic reactions and anaphylaxis.^{1,2,3} However recent publications have demonstrated that there are notable differences in the pharmacokinetic profiles of injection products.^{4,5,6} Despite these significant pharmacokinetic differences, all approved products are considered to have indistinguishable efficacy and similar safety profiles.
- Epinephrine auto-injectors (EAI) are the most frequently used products for out-of-hospital treatment; however, they are considered inconvenient and cumbersome, with up to 83% of patients/caregivers reporting they failed to administer or delayed the use of EAI, even when they know they are having a severe allergic reaction.^{7,8,9,10}
- neffy* is an intranasal (IN) epinephrine spray that is a needle-free alternative epinephrine delivery device being developed 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, making it easier to carry the product at all times and eliminating the risk of needle related injuries to the patient or caregiver.
- This study was conducted to evaluate the pharmacokinetics and pharmacodynamics of *neffy* compared with EpiPen 0.3 mg and manual intramuscular epinephrine 0.3 mg injection by needle and syringe (Epinephrine 0.3 mg IM).

METHODS

This was a Phase 1, six-treatment, six-period, single and repeat dose, crossover study conducted in 59 healthy subjects. The study was conducted in two parts, with single doses administered in Part 1 and repeated doses administered in Part 2.

Each subject in Part 1 was randomized to receive:

- a single dose of *neffy* 2.0 mg;
- a single dose of EpiPen 0.3 mg;
- a single dose of Epinephrine 0.3 mg IM.

Each subject in Part 2 was randomized to receive:

- two doses of *neffy* 2.0 mg both in the right nare (R/R);
- two doses of *neffy* 2.0 mg one in the left nare and one in the right nare (L/R);
- two doses of EpiPen 0.3 mg one into the left thigh and one into the right thigh (L/R).

Figure 1: Treatment Schedule



RESULTS

PHARMACOKINETIC RESULTS

- Following administration of a single dose (Figure 2), 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. Following repeated doses (Figure 2), mean epinephrine concentrations after administration of both the *neffy* treatments were higher compared to EpiPen through the entire sampling duration of 360 min.
- Following administration of a single dose (Table 1), 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 injection 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 injection (45.0 minutes).
- Following administration of a repeated dose (Table 1), mean C_{max} values were similar for all treatments with *neffy* (L/R) (1000 pg/mL), followed by *neffy* (R/R) (992 pg/mL) and EpiPen (840 pg/mL) with no statistical differences. The mean total exposure was lower following EpiPen (56900 min*pg/mL) relative to both *neffy* (R/R) (86,000 min*pg/mL) and *neffy* (L/R) (86000 min*pg/mL).

Figure 2: Mean Plasma Concentration versus Time Profiles

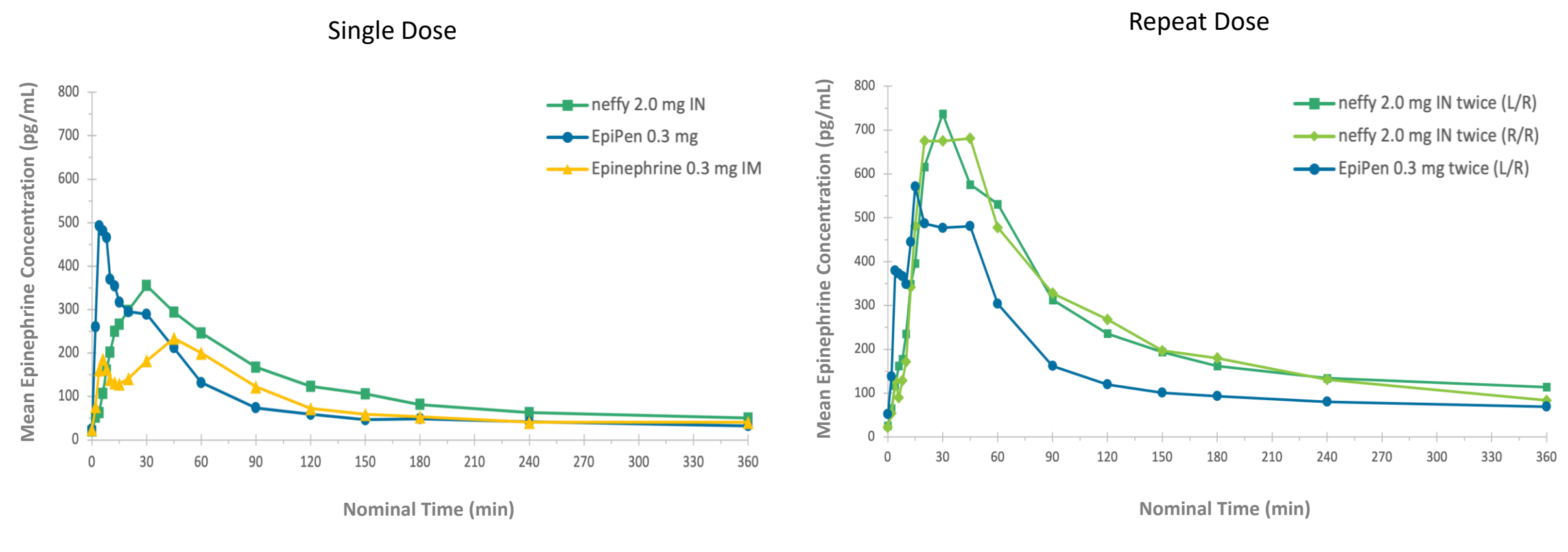


Table 1: Summary Statistics of Epinephrine Pharmacokinetic Parameters

Treatment	N	t _{max} (min) median (range)	C _{max} (pg/mL) mean (%CV)	AUC _{last} (min*pg/mL) mean (%CV)
Single Dose				
<i>neffy</i> 2.0 mg	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 IM 0.3 mg	42	45.0 (4.00 – 90.0)	339 (74.1)	29300 (41.7)
Repeat Dose				
<i>neffy</i> 2.0 mg (L/R)	39	30.0 (6.00 – 150)	1000 (93.1)	86000 (77.0)
<i>neffy</i> 2.0 mg (R/R)	39	30.0 (4.00 – 150)	992 (75.3)	86000 (60.5)
EpiPen 0.3 mg (L/R)	42	15.0 (0.00 – 360)	840 (60.6)	56900 (52.1)

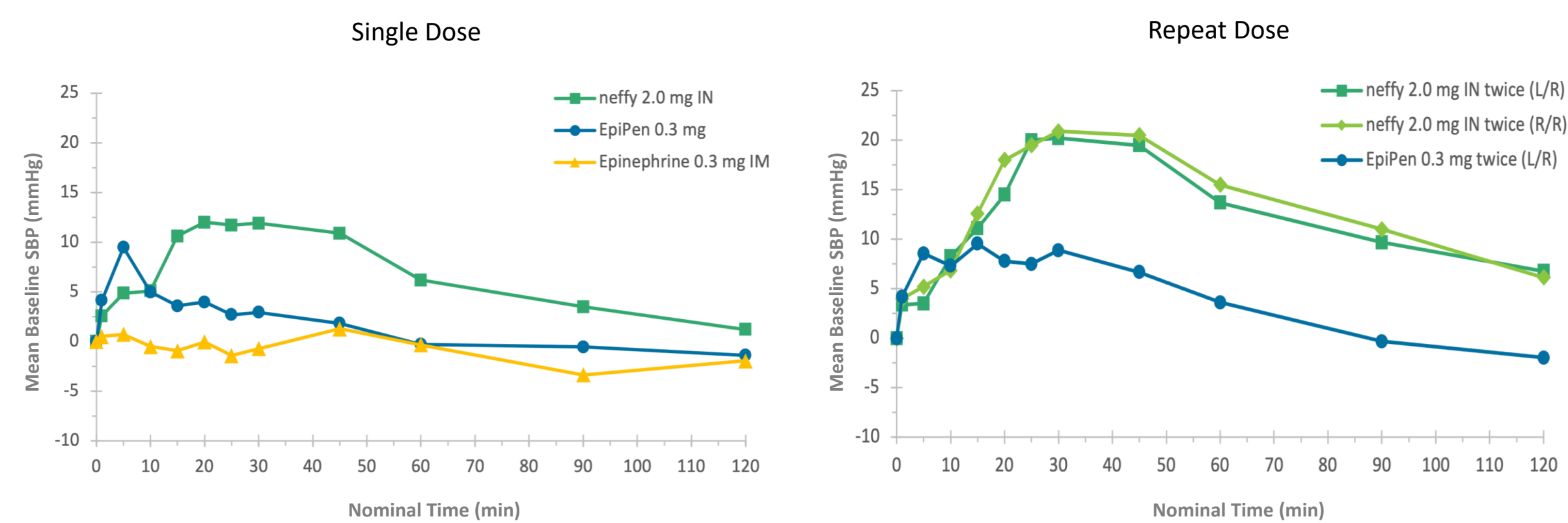
C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration; AUC_{last} = area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation

PHARMACODYNAMIC RESULTS

SYSTOLIC BLOOD PRESSURE (Figure 3 and Table 2)

- Following a single dose, all treatments resulted in an increase from baseline SBP, with the greatest mean 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 0.3 mg IM. Mean SBP E_{max} was higher following *neffy* relative to both EpiPen and Epinephrine IM injection.
- Following repeated doses, the change from baseline SBP was higher for *neffy* treatments compared to EpiPen. Mean E_{max} was significantly higher after both *neffy* (R/R) and *neffy* (L/R) relative to EpiPen. Mean E_{max} between *neffy* (R/R) and *neffy* (L/R) were not significantly different from each other.

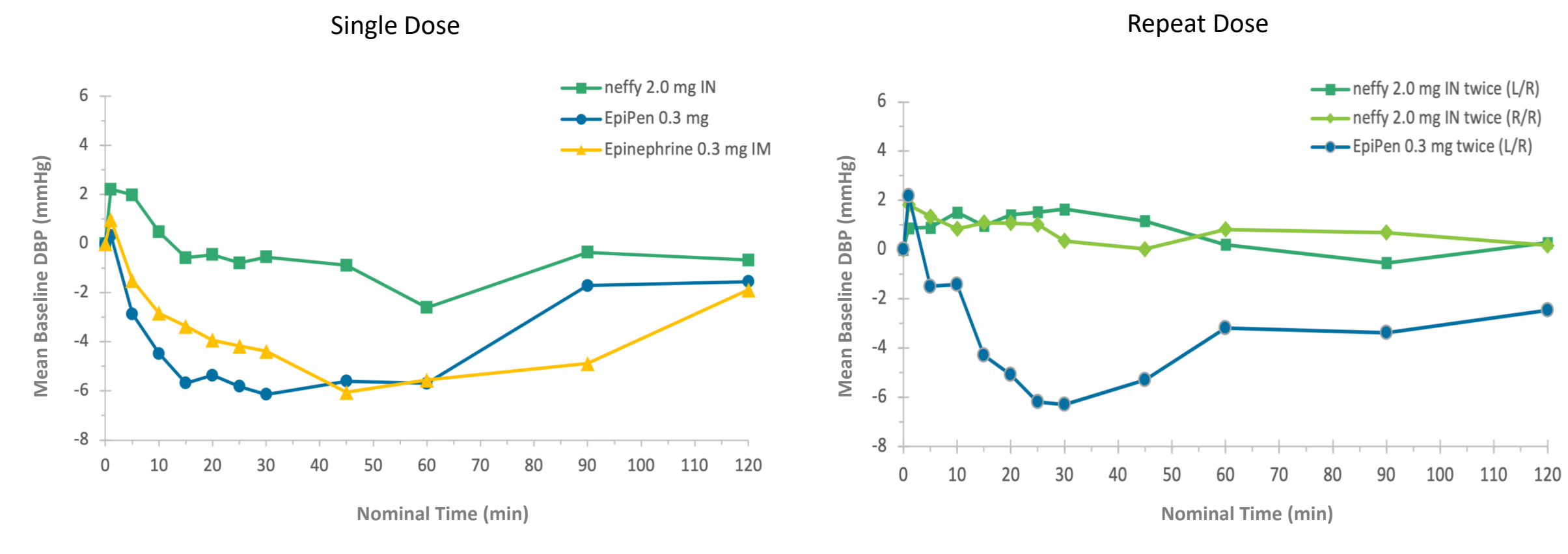
Figure 3: Mean Change from Baseline Systolic Blood Pressure versus Time Profiles



DIASTOLIC BLOOD PRESSURE (Figure 4 and Table 2)

- Following a single dose, *neffy* resulted in an initial increase from baseline DBP, followed by a decrease from baseline. Both EpiPen and Epinephrine IM injection resulted in an immediate decrease from baseline DBP. The decrease from baseline was markedly more pronounced following EpiPen and Epinephrine IM injection relative to *neffy*. Mean DBP E_{max} was significantly different following *neffy* relative to IM Epinephrine and EpiPen.
- Following repeated doses, both *neffy* treatments resulted in initial increase from baseline DBP, followed by a return towards baseline. EpiPen resulted in an immediate decrease from baseline DBP that persisted throughout the 120-minute timepoint. Mean DBP E_{max} was significantly higher following both *neffy* (R/R) and *neffy* relative to EpiPen (L/R). There were no significant differences between *neffy* (R/R) and *neffy* (L/R).

Figure 4: Mean Change from Baseline Diastolic Blood Pressure versus Time Profiles



HEART RATE (Figure 5 and Table 2)

- Following a single dose, all treatments resulted in increases from baseline HR. There was a return towards baseline after both Epinephrine IM injection 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 injection.
- Following repeated doses, all three treatments resulted in an increase from baseline HR. Overall, *neffy* (R/R) and *neffy* (L/L) resulted in more pronounced increases from baseline relative to EpiPen. Mean HR E_{max} was significantly higher following *neffy* (R/R) and *neffy* (L/R) relative to EpiPen. There were no significant differences between *neffy* (R/R) and *neffy* (L/R).

Figure 5: Mean Change from Baseline Heart Rate versus Time Profiles

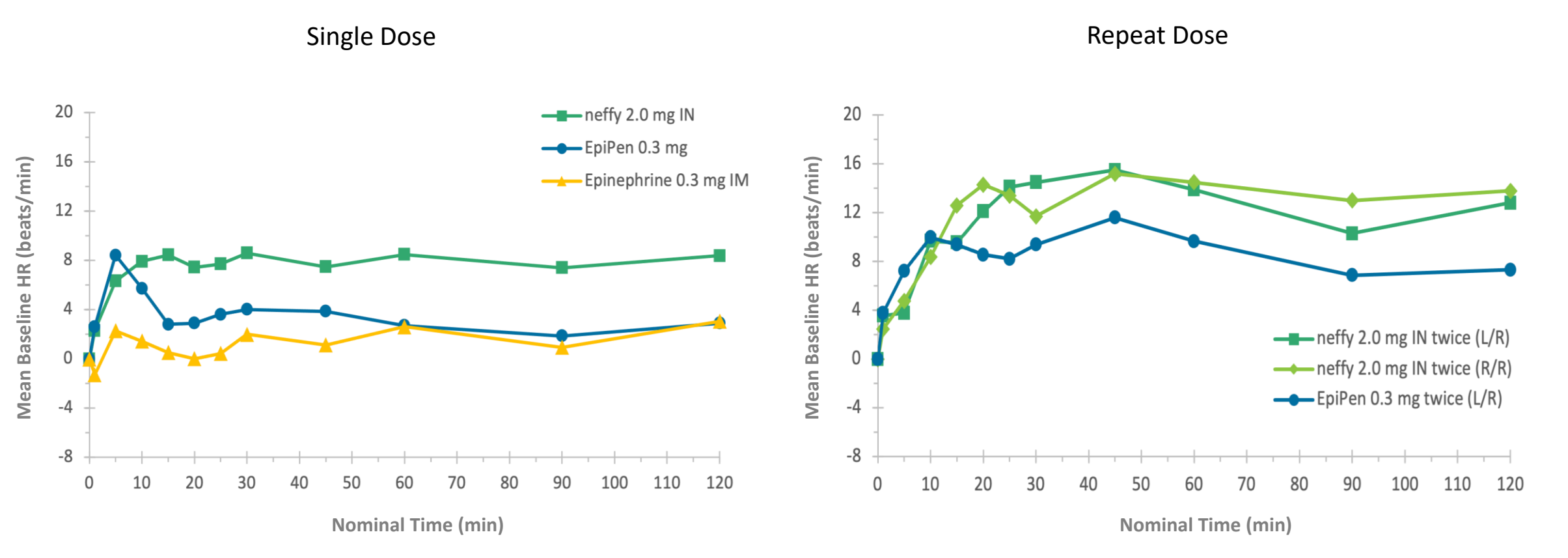


Table 2: Maximum Pharmacodynamic Effect (Change from Baseline) and Time to Maximum Pharmacodynamic Effect

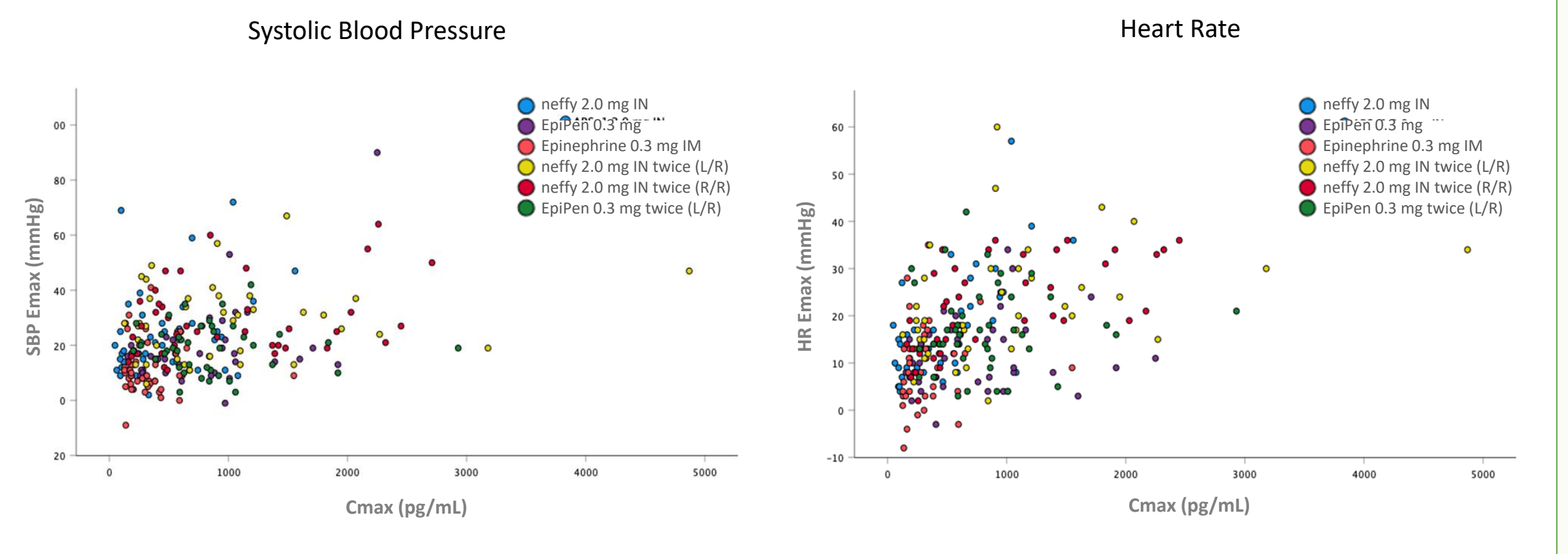
Treatment	N	Mean E _{max} (SD)			Median T _{Emax} (min)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP	DBP	HR
Single Dose							
neffy 2.0 mg	42	23.6 (64.8)	8.10 (64.3)	17.3 (62.7)	25.0 (1.00 – 116)	13.0 (1.00 – 117)	19 (1.00 – 116)
EpiPen 0.3 mg	42	18.2 (80.3)	5.62 (131)	12.3 (63.2)	9.0 (1.00 – 116)	10.0 (1.00 – 115)	10.0 (1.00 – 115)
Epinephrine IM 0.3 mg	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)
Repeat Dose							
neffy 2.0 mg (L/R)	39	28.9 (47.0)	10.5 (71.2)	22.1 (55.0)	29.0 (2.00 – 116)	19.0 (1.00 – 115)	29.0 (1.00 – 116)
neffy 2.0 mg (R/R)	39	29.1 (46.0)	9.62 (83.5)	22.9 (44.3)	28.0 (6.00 – 85.0)	13.0 (1.00 – 118)	40.0 (1.00 – 116)
EpiPen 0.3 mg (L/R)	42	19.1 (46.0)	6.31 (89.6)	17.4 (51.6)	15.5 (1.00 – 85.0)	5.00 (1.00 – 115)	24.5 (1.00 – 116)

E_{max} = maximum effect; T_{Emax} = time to maximum effect; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

PHARMACODYNAMIC/PHARMACOKINETIC RESULTS (Figure 6)

Scatterplots of individual subject responses were generated to investigate the relationship between E_{max} and C_{max} for SBP and HR. The highest SBP E_{max} was observed following EpiPen, and the highest HR E_{max} was observed following *neffy* (L/R).

Figure 6: Individual Subject Responses Systolic Blood Pressure (E_{max} versus C_{max})



SAFETY RESULTS

The study treatments were well tolerated, and all treatment emergent adverse event were considered mild.

DISCUSSION

- neffy* 2.0 mg was designed to have a PK profile that is within the range of currently approved injection products (Epinephrine 0.3 mg IM and EpiPen 0.3 mg). The present data demonstrates that *neffy*'s PD profile is comparable to EpiPen 0.3 mg and is comparable to or better than Epinephrine 0.3 mg IM, suggesting that *neffy* may be at least as efficacious as these approved products.
- Despite having a lower C_{max} relative to EpiPen, *neffy*, dosed both once or twice, resulted in more pronounced mean increases in SBP, DBP, and HR. One of the mechanisms by which this likely occurs involves *neffy*'s absorption by the intranasal route which bypasses the powerful β₂-mediated vasodilatation caused by IM injection into the skeletal muscle.¹¹ In contrast to IN administration via *neffy*, injection into the thigh directly exposes skeletal muscle to the full dose of epinephrine, resulting in the activation of the β₂ receptors that are abundantly located in the skeletal muscle. This β₂ activation results in vasodilatation and a subsequent decrease in peripheral vascular resistance, ultimately resulting in a rapid decrease in DBP.¹² Despite *neffy* having a higher mean increase in SBP the most extreme increases were observed with EpiPen due to very early spikes in epinephrine plasma concentrations that may be due to direct injection into a blood vessel (i.e., IV bolus administration).
- neffy* also had the most robust and efficient effect on heart rate despite its lower C_{max} relative to EpiPen. The mechanism by which occurs is likely related to the complicated interaction between adrenergic receptor subtypes as well as the relationship between blood pressure and heart rate. It is known that β receptors have higher affinity and activated at lower epinephrine concentration, therefore it is expected that heart rate would be correlated with epinephrine concentration, meaning the increase should be most pronounced after EpiPen administration. The current finding that *neffy* results in a greater increase in heart rate relative to EpiPen, considering the difference in PK profiles, has been observed throughout the clinical development program. One potential explanation is that the rapid increase in plasma epinephrine concentrations following EpiPen, and to a lesser extent, IM epinephrine, results in a rapid increase in heart rate via activation of the β₁ receptors (positive inotropic and chronotropic actions). This rapid increase in heart rate that would increase blood pressure may then activate compensatory reflexes, such as baroreceptor reflex, which is responsible for dynamic changes for second-to-second monitoring and maintenance of blood pressure and heart rate.¹³
- The activation of the baroreceptor reflex by the sudden increase in HR and blood pressure following epinephrine injection would act to suppress the increase in heart rate. In contrast, the slightly slower absorption of *neffy* does not cause a sudden rise in SBP, therefore the baroreceptor reflex is not activated and there is no secondary inhibition of heart rate. This may be supported by the finding that despite having the highest C_{max}, EpiPen does not result in the maximum HR E_{max} (Figure 6).

CONCLUSION

This study demonstrated that the pharmacokinetics of *neffy* are within the range of other approved epinephrine products. *neffy* results in a more robust PD responses compared to injection products, in part because intranasal administration bypasses the high-affinity β₂-receptors in the skeletal muscle of the thigh, thus mitigating the β₂ mediated vasodilatation and subsequent compensatory responses such as baroreceptor. While the mean SBP and HR responses were greater with *neffy* compared to EpiPen, the most extreme changes in SBP and HR were observed with EpiPen, presumably due to direct or partial injection into blood vessels. *neffy*'s safety profile is comparable to other approved epinephrine products, but lacks the needle related risk to both the patient and caregiver, including possible injection into blood vessels. These results 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.

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