Pediatric Doses of *neffy* (epinephrine nasal spray) Demonstrate Pharmacokinetic Profiles Equivalent to Epinephrine Injection Products

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RATIONALE

Epinephrine is the first-line treatment for severe allergic reactions, including anaphylaxis[1,2]. Despite epinephrine's well documented history of safety and efficacy, patients/caregivers frequently fail to treat or delay treating severe allergic reactions, citing challenges of carrying epinephrine auto-injectors and concerns about injection. These concerns are particularly pronounced in pediatric patients, who, along with their caregivers, tend to be more anxious about injectable devices. An intranasal epinephrine spray (*neffy*) is being developed as a needle-free option for the treatment of severe allergic reactions.

neffy is an intranasal (IN) epinephrine delivery device being developed for the emergency treatment of (Type I) allergic reactions, including anaphylaxis. *neffy's* pharmacokinetic and pharmacodynamic profiles have been repeatedly demonstrated to be within the range of approved injection and it is anticipated that *neffy* will provide a safe and effective treatment option, particularly for patients/caregivers who are reluctant to use injectable devices.

This study was conducted to evaluate *neffy's* pharmacokinetic, pharmacodynamic, and safety profiles in pediatric allergy patients receiving neffy 1 mg or 2 mg, based on body weight.

METHODS

This was a randomized, single-dose, phase 1 pharmacokinetic study conducted in 42 pediatric allergy patients. Patients weighing 15-30 kg (N=21) received neffy 1 mg and patients weighing ≥30 kg (N=21) received neffy 2 mg (**Table 1**). Subjects were required to have a history of significant systemic (Type 1) allergies to food, insects, venom, or drugs that required that the subject or caregiver been prescribed an epinephrine product for reversal of symptoms if exposed to an antigen.

Pharmacokinetic and pharmacodynamic (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate [PR]) parameters were evaluated. Safety assessments included adverse events (AEs), vital signs, and physical examinations.

Table 1: Study Participants

Age (range)	Males	Females	Height mean (SD)	Weight mean (SD)	Body Mass Index mean (SD)
15-30 kg 4-11 Years Old	13 (62.0%)	8 (38.0%)	128.0 (7.6) cm	25.0 (3.6) kg	15.0 (1.4) kg/m^2
≥30 kg 8-17 Years Old	12 (57.0%)	9 (43.0%)	165.0 (12.7) cm	54.0 (14.0) kg	20.0 (3.2) kg/m^2

RESULTS

PHARMACOKINETIC RESULTS (Figure 1 & Table 2)

The mean maximum epinephrine concentration (C_{max}) values were 651 pg/ml (15 – 30 kg subjects receiving neffy 1.0 mg) and 690 pg/mL (≥30 kg subjects receiving neffy 2.0 mg).

The median time to reach C_{max} (T_{max}) values were 20.0 minutes (15 – 30 kg subjects receiving neffy 1.0 mg) and 29.5 minutes (≥30 kg subjects receiving neffy 2.0 mg).

Mean total exposure (AUC_{0-t}) values were 35100 min*pg/mL (15 – 30 kg subjects receiving neffy 1.0 mg) and 40200 min*pg/mL (≥30 kg subjects receiving neffy 2.0 mg).

Mean (SE) epinephrine concentrations curves over time, by weight/dose group are presented in **Figure 1** and pharmacokinetic parameters by weight/dose group are presented in **Table 2**.

PHARMACODYNAMIC RESULTS (Figure 2 & Table 3)

Systolic Blood Pressure: The mean maximum effect (E_{max}) and median time to reach E_{max} (TE_{max}) were 13.4 mmHg and 20.0 minutes (15 – 30 kg subjects receiving *neffy* 1.0 mg) and 12.2 mmHg and 25.0 minutes (≥30 kg subjects receiving *neffy* 2.0 mg).

Diastolic Blood Pressure: The mean E_{max} and median TE_{max} were 7.00 mmHg and 15.0 minutes (15 – 30 kg subjects receiving *neffy* 1.0 mg) and 8.67 mmHg and 25.0 minutes (≥30 kg subjects receiving *neffy* 2.0 mg).

Pulse Rate: The mean E_{max} and median TE_{max} were 18.5 bpm and 25.0 minutes (15 – 30 kg subjects receiving *neffy* 1.0 mg) and 16.9 bpm and 44.0 minutes (≥30 kg subjects receiving *neffy* 2.0 mg).

The pharmacodynamic response (change from baseline) over time is presented in **Figure 2** and a summary of pharmacodynamic parameters is presented in **Table 3**.

SAFETY RESULTS

The majority of adverse events were mild; none were serious or resulted in discontinuation from the study.

CONCLUSIONS

Pediatric doses of *neffy* have a favorable safety profile with pharmacokinetic and pharmacodynamic profiles within range of approved injection products. *neffy* is expected to be a safe and effective option for the treatment of severe allergic reactions and anaphylaxis in pediatric patients.

neffy 1.0 mg (15-30 kg) and 2.0 mg (≥30 kg) **are expected to be safe and effective options for the treatment of severe allergic reactions and anaphylaxis in pediatric patients.**

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Table 2: Pharmacokinetic Parameters by Weights/Dose

Weight Group/ Dose	N	C_{max} (pg/mL) mean (%CV)	t_{max} (min) median (range)	AUC_{0-t} (min*pg/mL) mean (%CV)
neffy 1.0 mg (15-30 kg)	21	651 (64.2)	20.0 (2.50 – 61.5)	35100 (57.3)
neffy 2.0 mg (≥30 kg)	21	690 (100)	29.5 (2.90 – 120)	40200 (92.8)

Figure 1: Mean (SE) Epinephrine Concentration Curves Over Times by Weight/Dose

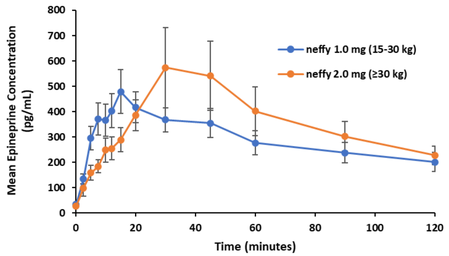
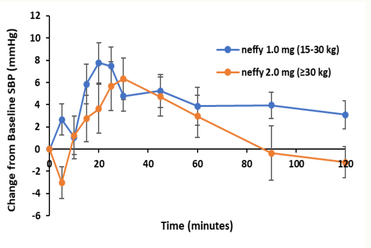
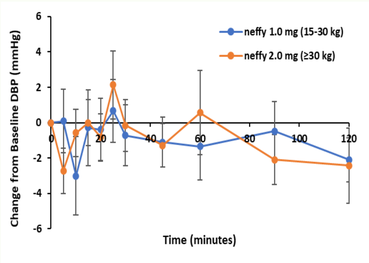


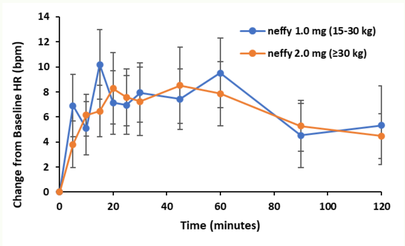
Table 3: Summary Statistics of Epinephrine Pharmacodynamics Parameters

Weight Group/ Dose	N	Mean E_{max} (CV%)			Median T_{Emax} (range)		
		SBP (mmHg)	DBP (mmHg)	PR (bpm)	SBP (min))	DBP (min)	PR (min)
neffy **2.0 mg** ***(15 – 30 kg)***	21	13.4	7	18.5	20	15	25
		-44.6	-97.9	-63.5	(11.0 – 122)	(4.00 – 117)	(4.00 – 120)
neffy **2.0 mg** ***(≥30 kg)***	21	12.2	8.67	16.9	25	25	44
		-67.4	-108	-64.1	(14.0 – 90.0)	(9.00 – 120)	(5.00 – 120)

Figure 2: Pharmacodynamics Response (Change from baseline) Over Time







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