Presentation ID: P018

A Single-Period, Single-Dose Study of the Pharmacokinetics of Epinephrine After Administration of 2.0 mg Intranasal ARS-1 (neffy® Nasal Spray) to Pediatric Subjects with a History of Allergic Reactions

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RATIONALE

- Epinephrine has a long and well-documented history of safety and efficacy; however, a significant proportion of patients/caregivers are reluctant to administer epinephrine injections, even when they/their child are/is having a severe reaction.[1,2] Patients/caregivers who delay or fail to treat often cite concerns about carrying the device and fears about the injection. These concerns are particularly pronounced in pediatric patients, who, along with their caregivers, tend to be more anxious about injectable devices.
- *neffy* is an intranasal (IN) epinephrine spray which is 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.
- The current study was conducted to evaluate *neffy's* pharmacokinetic, pharmacodynamic, and safety profiles in pediatric allergy patients. Pediatric pharmacokinetic and pharmacodynamic data was considered relative to adult data from another ARS clinical trial.[3]

METHODS

This is a Phase 1, single-dose, single-treatment study in 21 pediatric allergy subjects ≥30 kg. 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 be 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 heart rate [HR]) parameters were evaluated. Safety assessments included adverse events (AEs), vital signs, and physical exams.

Those results were compared with the response to *neffy* 2.0 mg in adults.[3]

Pediatric subjects ranged in age from 8 to 17 years, with a mean (SD) age of 14.1 (2.4) years. Twelve subjects (57.1%) were male, and nine subjects (42.9%) were female. Subjects had a mean (SD) height of 164.8 (12.7) cm, a mean (SD) weight of 54.1 (13.5) kg, and a mean (SD) body mass index of 19.7 (3.2) kg/m2.

One subject (01-111) had a maximum epinephrine concentration (C_{max}) of 3300 pg/mL and was considered a PK outlier. The maximum change from baseline PD values were 11 mmHg for SBP, 4 mmHg for DBP, and 27 bpm for HR. This subject was excluded from the PK analysis but was not excluded from the PD analysis.

RESULTS

PHARMACOKINETIC RESULTS (Figure 1, Table 1)

When administered to pediatric subjects ≥30 kg, neffy 2.0 mg resulted in epinephrine concentrations consistent with that observed in adults (Figure 1). Pharmacokinetic parameters also demonstrated comparable pharmacokinetics between pediatric and adult subjects (Table 1).

PHARMACODYNAMIC RESULTS (Figure 2)

Pediatric subjects had a lower baseline blood pressure and higher baseline heart rate relative to adult subjects. In both adult and pediatric subjects, administration of neffy 2.0 mg resulted in increases in SBP and HR. The magnitude of the heart rate increase was similar between adult and pediatric subjects, however the SBP increase was more pronounced in adults (Figure 2 and Table 2). While there was initial increase in DBP in adult subjects, an initial and transient drop was observed in pediatric subjects, which may have contributed the corresponding transient drop in SBP.

SAFETY RESULTS

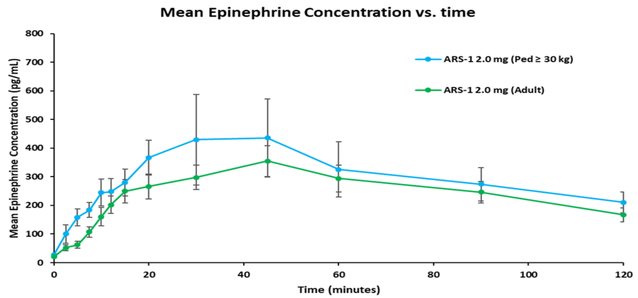
Most adverse events were mild; none were serious or resulted in discontinuation from the study.

CONCLUSIONS

Administration of neffy 2.0 mg to pediatric subjects ≥30 kg resulted in a pharmacokinetic profile that was similar to what has previously been observed in adults. The heart rate response in pediatric subjects was comparable to what has been observed in adults. The systolic blood pressure response was less pronounced in pediatric subjects; however, this finding is consistent with the differences in the developmental physiology of the cardiovascular system and with the response to epinephrine, regardless of route of administration.[4,5]

The results of this study demonstrate that neffy 2.0 mg is likely to be a safe and effective option for the treatment of severe allergic reactions, including anaphylaxis, in children ≥30 kg. The availability of a needle-free device is particularly important for children and their caregivers, who tend to be more anxious about injectable devices.

Figure 1: Mean (SE) Epinephrine Concentration vs Time: Mean (SE) Epinephrine Concentration versus Time



neffy 2.0 mg, epinephrine nasal spray, is a safe and effective option for the treatment of severe allergic reactions, including anaphylaxis, in children ≥30 kg

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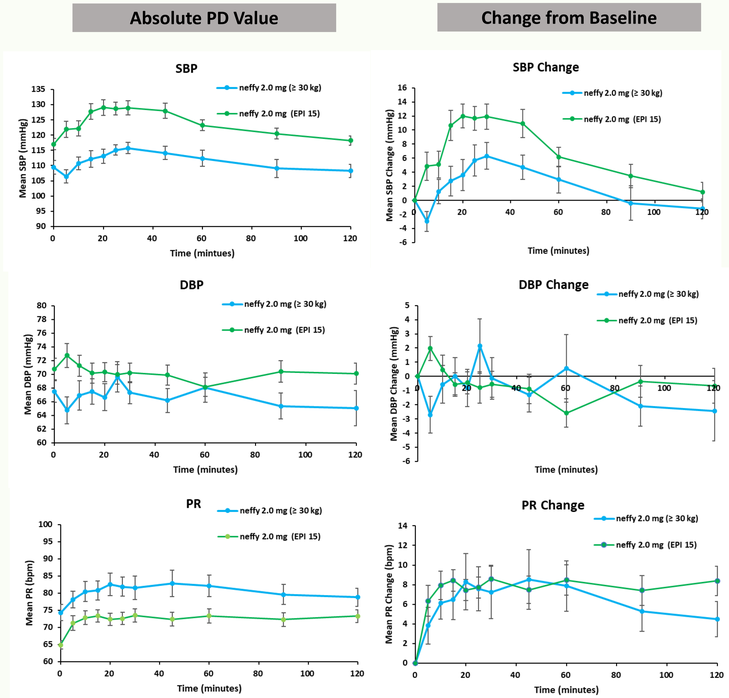
Table 1: Summary Statistics of Epinephrine Pharmacokinetic Parameters

Treatment	N	C_{max} (pg/mL) mean (%CV)	t_{max} (min) median (range)	AUC_{0-t} (min*pg/mL) mean (%CV)	pAUC (min*pg/mL) mean (%CV)		
					$pAUC_{0-15}$	$pAUC_{0-60}$	$pAUC_{0-118}$* $pAUC_{0-120}$**
Pediatric Subjects ≥ 30 kg							
neffy 2.0 mg	20	560 (63.7)	29.5 (2.9 – 120)	34393 (77.4)	2713 (70.6)	20957 (70.4)	37559 (70.6)
Adult Subjects							
neffy 2.0 mg	42	481 (76.0)	30.0 (6.00 – 150)	43500 (69.4)	2200 (95.4)	15700 (82.7)	26300 (80.3)

* $pAUC_{0-118}$ was calculated for pediatric subjects
** $pAUC_{0-120}$ was calculated for adult subjects

Figure 2: Pharmacodynamic Response to neffy



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Presented at the Annual Scientific Meeting of the American College of Allergy, Asthma and Immunology (ACAAI); November 9-13, 2023; Anaheim, CA

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