Pharmacokinetics and Pharmacodynamics of ARS-1 (*neffy* Nasal Spray) and Manual Intramuscular Injection in Subjects With/Without Allergic Rhinitis

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RATIONALE

- ***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. ***neffy*** is anticipated to have pharmacokinetic, pharmacodynamic, and safety profiles that are within the range of currently approved epinephrine injection products.
- Given its IN administration, it is important to assess the impact that nasal symptoms such as sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion have on ***neffy***'s absorption.
- This study was conducted to evaluate the pharmacokinetics and pharmacodynamics of ***neffy*** (under normal conditions and with induced rhinitis) and manual intramuscular (IM) injection (0.3 mg and 0.5 mg) in subjects with seasonal allergies. Rhinitis with subsequent rhinorrhea when dosed in an upright sitting position is considered the worse case situation for intranasal administration.

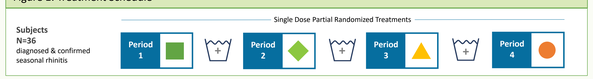
METHODS

This was a Phase 1, single-dose, four-period, partially randomized, cross-over study in 36 subjects with diagnosed and confirmed seasonal rhinitis. Pharmacokinetic and pharmacodynamic profiles were evaluated. All subjects were dosed in an upright sitting position.

Each subject received each of the following:

- a single 2.0 mg/100 µL IN dose of ***neffy*** in the naris with normal nasal conditions (***neffy*** 2.0 mg IN);
- a single 2.0 mg/100 µL IN dose of ***neffy*** in the naris with induced rhinitis (***neffy*** 2.0 mg IN with Rhinitis);
- a single 0.3 mg IM injection dose of epinephrine with standard needle and syringe in the anterolateral thigh with normal conditions (Epinephrine 0.3 mg IM);
- a single 0.5 mg IM injection dose of epinephrine with standard needle and syringe in the anterolateral thigh with normal conditions (Epinephrine 0.5 mg IM) in a cross over manner.

Figure 1: Treatment Schedule



RESULTS

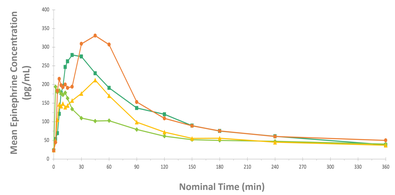
A total of 36 subjects were enrolled, with 34 subjects completing all dosing arms in the study. All 36 subjects received at least one dose of study drug. Subjects ranged in age from 20 to 52 years. Twenty subjects (55.6%) were male, and 16 subjects (44.4%) were female.

PHARMACOKINETIC RESULTS

CONCENTRATION-TIME (Figure 2)

- Mean epinephrine concentrations resulted in a higher C_{max} and more rapid t_{max} following ***neffy*** with normal nasal conditions relative to Epinephrine 0.3 mg and 0.5 mg IM. Mean peak epinephrine concentrations following ***neffy*** with rhinitis appeared to occur faster than other treatments evaluated. The overall exposure (AUC_{0-t}) of ***neffy*** was bracketed by the 0.3 mg and 0.5 mg IM injection doses.

Figure 2: Mean Epinephrine Concentration versus Time Profiles



PHARMACOKINETIC PARAMETERS (Table 1)

- Mean C_{max} values were highest after ***neffy*** 2.0 mg with normal nasal conditions (491 pg/mL), followed by Epinephrine 0.5 mg IM (452 pg/mL), ***neffy*** 2.0 mg with rhinitis (309 pg/mL), and Epinephrine 0.3 mg IM (283 pg/mL).
- Median t_{max} values were fastest following ***neffy*** 2.0 mg with rhinitis (6.00 minutes), followed by ***neffy*** 2.0 mg with normal nasal conditions (20.0 minutes). Median t_{max} values were 45.0 minutes for both the Epinephrine 0.3 mg and 0.5 mg IM doses.
- The greatest total exposure was observed after Epinephrine 0.5 mg IM (42400 min*pg/mL), followed by ***neffy*** 2.0 mg with normal nasal conditions (37100 min*pg/mL), Epinephrine 0.3 mg IM (27700 min*pg/mL), and ***neffy*** 2.0 mg with rhinitis (23500 min*pg/mL).

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)
neffy 2.0 mg IN	36	20.0 (2.00 – 120)	491 (65.2)	37100 (66.1)
neffy 2.0 mg IN with Rhinitis	33	6.0 (2.00 – 90.0)	309 (66.2)	23500 (69.1)
Epinephrine IM 0.3 mg	31	45.0 (4.00 – 60.0)	283 (54.9)	27700 (37.5)
Epinephrine IM 0.5 mg	31	45.0 (4.00 – 360)	452 (81.1)	42400 (40.2)

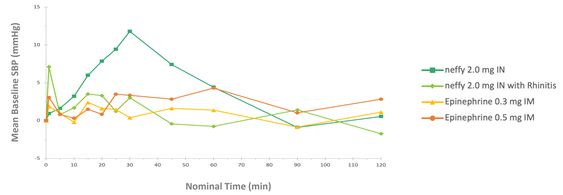
C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration; AUC_{last} = area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation

PHARMACODYNAMIC RESULTS

SYSTOLIC BLOOD PRESSURE (Figure 3 and Table 2)

- Mean SBP E_{max} values were highest following ***neffy*** 2.0 mg with normal nasal conditions (20.8 mmHg), followed by Epinephrine 0.5 mg IM (15.2 mmHg), ***neffy*** 2.0 mg with rhinitis (15.0 mmHg), and Epinephrine 0.3 mg IM (13.4 mmHg).
- The longest median SBP T_{Emax} was observed following Epinephrine 0.5 mg IM (30.0 minutes) followed by ***neffy*** 2.0 mg with normal nasal conditions (20.0 minutes), and ***neffy*** 2.0 mg with rhinitis and Epinephrine 0.3 mg IM (both 19.0 minutes).
- Overall effect as measured by mean $AUEC_{last}$ was highest following ***neffy*** 2.0 mg with normal nasal conditions (695 min*mmHg), followed Epinephrine 0.5 mg IM (615 min*mmHg), Epinephrine 0.3 mg IM (395 min*mmHg), and ***neffy*** 2.0 mg with rhinitis (377 min*mmHg).

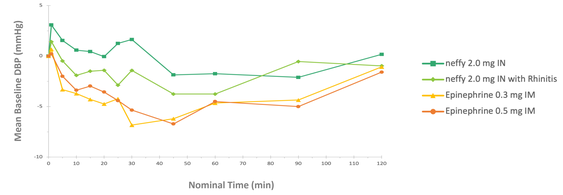
Figure 3: Mean Change from Baseline Systolic Blood Pressure versus Time Profiles



DIASTOLIC BLOOD PRESSURE (Figure 4 and Table 2)

- The longest median DBP T_{Emax} was observed following ***neffy*** 2.0 mg with rhinitis and Epinephrine 0.5 mg IM (both 26.0 minutes), followed by ***neffy*** 2.0 mg with normal nasal conditions (25.0 minutes), and Epinephrine 0.3 mg IM (14.0 minutes).
- Mean DBP E_{max} values were highest following ***neffy*** 2.0 mg (normal nasal conditions) (10.0 mmHg), followed by ***neffy*** 2.0 mg with rhinitis (7.15 mmHg), Epinephrine 0.5 mg IM (5.69 mmHg), and Epinephrine 0.3 mg IM (5.26 mmHg).
- Overall effect as measured by mean $AUEC_{last}$ was positive following ***neffy*** 2.0 mg (normal nasal conditions) (156 min*mmHg) and ***neffy*** 2.0 mg with rhinitis) (47.7 min*mmHg), and negative following Epinephrine 0.3 mg IM (- 94.5 min*mmHg), Epinephrine 0.5 mg IM (-65.7 min*mmHg).

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



HEART RATE (Figure 5 and Table 2)

- The longest median HR T_{Emax} was observed following Epinephrine 0.3 mg IM (44.0 minutes), followed by ***neffy*** 2.0 mg with normal nasal conditions (25.0 minutes), Epinephrine 0.5 mg IM (19.5 minutes), and ***neffy*** 2.0 mg with rhinitis (4.00 minutes).
- Mean HR E_{max} values were highest following ***neffy*** 2.0 mg with normal nasal conditions (18.5 bpm), followed by Epinephrine 0.5 mg IM (13.6 bpm), Epinephrine 0.3 mg IM (11.1 bpm), and ***neffy*** 2.0 mg with rhinitis (10.8 bpm).
- Overall effect as measured by mean $AUEC_{last}$ was highest following ***neffy*** 2.0 mg with normal nasal conditions (886 min*bpm), followed by Epinephrine 0.5 mg IM (560 min*bpm), Epinephrine 0.3 mg IM (433 min*bpm), and ***neffy*** 2.0 mg with rhinitis (220 min*bpm).

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

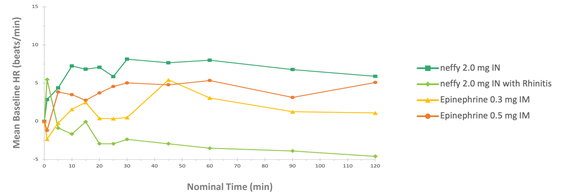


Table 2: Maximum Pharmacodynamic Effect (Change from Baseline) and Time to Maximum Pharmacodynamic Effect

Treatment	N	Mean E_{max} (SD)			Median T_{Emax} (min)		
		SBP (mmHg)	DBP (mmHg)	HR (bpm)	SBP	DBP	HR
neffy 2.0 mg IN	36	20.8 (80.6)	10.0 (77.2)	18.5 (75.9)	26.0 (1.00 – 120)	25.0 (1.00 – 120)	25.0 (1.00 – 178)
neffy 2.0 mg IN with Rhinitis	33	15.0 (84.5)	7.15 (95.8)	10.8 (114)	19.0 (1.00 – 120)	26.0 (1.00 – 119)	4.00 (1.00 – 119)
Epinephrine IM 0.3 mg	31	13.4 (70.9)	5.26 (141)	11.1 (73.3)	19.0 (1.00 – 123)	14.0 (1.00 – 123)	44.0 (2.00 – 120)
Epinephrine IM 0.5 mg	32	15.2 (62.3)	5.69 (104)	13.6 (54.0)	30.0 (1.00 – 120)	26.0 (1.00 – 120)	19.5 (1.00 – 122)

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

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS (Figure 6)

SYSTOLIC BLOOD PRESSURE

- There was a positive relationship between epinephrine concentration and change from baseline SBP for all treatments except for Epinephrine 0.3 mg IM.
- The slope for the SBP change from baseline vs. epinephrine concentration was the greatest following ***neffy*** with normal conditions (0.0258) followed by ***neffy*** with rhinitis (0.0119), Epinephrine 0.5 mg IM (0.0073), and Epinephrine 0.3 mg IM (-0.0076).

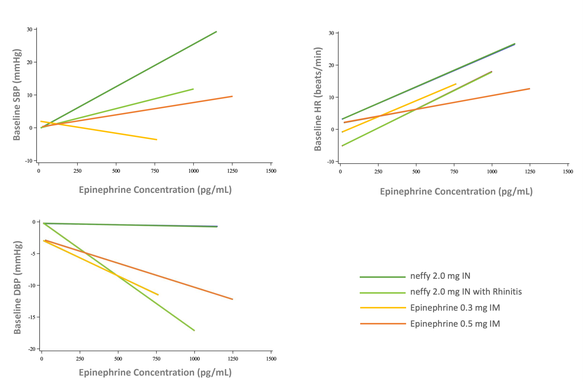
DIASTOLIC BLOOD PRESSURE

- There was a negative relationship between epinephrine concentration and change from baseline DBP for all treatments.
- The negative slope for the DBP change from baseline vs. epinephrine concentration was the least pronounced following ***neffy*** with normal conditions (- 0.0004), followed by Epinephrine 0.5 mg IM (-0.0076), and Epinephrine 0.3 mg IM (-0.0114), and ***neffy*** with rhinitis (- 0.0172).

HEART RATE

- The slope for HR change from baseline vs. epinephrine concentration was the greatest following ***neffy*** with rhinitis (0.0234) followed by ***neffy*** with normal conditions (0.0205), Epinephrine 0.5 mg IM (0.0086), and Epinephrine 0.3 mg IM (0.0199).

Figure 6: Fitted Change from Baseline PD Parameters versus Epinephrine Concentration



SAFETY RESULTS

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

DISCUSSION

PHARMACOKINETICS

- This study demonstrated that rhinitis resulted in more rapid absorption due to nasal symptoms including mucosal oedema.
- This more rapid absorption resulted in a more rapid t_{max} (6 min with oedema vs. 20.5 min without oedema), however, it also resulted in a decrease of approximately 35% in C_{max}. Considering that symptoms of rhinitis include rhinorrhea, rhinorrhea may have helped clear the drug more quickly from the nasal mucosa where absorption occurs.
- While this study serves as worst case scenario of ***neffy*** pharmacokinetics during allergic reactions that include nasal rhinorrhea symptoms and dosed in an upright sitting position, it is important to note that the decreased C_{max} associated with rhinitis was still comparable to the C_{max} of Epinephrine 0.3 mg IM with normal conditions, which is well known to be efficacious.

PHARMACODYNAMICS

- Under normal nasal conditions, ***neffy*** resulted in more pronounced changes in SBP, DBP, HR relative to Epinephrine 0.3 mg IM and comparable SBP and HR to Epinephrine 0.5 mg IM. The result was consistent with previous reports.
- ***neffy*** with rhinitis resulted smaller increases in SBP and DBP relative to ***neffy*** with normal nasal conditions, but for both SBP and DBP, these changes were still comparable to the PD responses following Epinephrine 0.3 mg and 0.5 mg IM. Increase in HR following ***neffy*** with rhinitis was comparable to Epinephrine 0.3 mg IM through 30 minutes after dosing.
- Following both Epinephrine IM 0.3 and 0.5 mg, there was a negative relationship between epinephrine concentration and change from baseline DBP, a finding that is consistent with previous reports suggesting that IM injection may suppress the increase in SBP by causing a drop in DBP through activation of the β_2-receptors in the skeletal muscles. This effect is not observed following ***neffy***, presumably because IN administration bypasses direct injection into skeletal muscle.
- While ***neffy*** with normal nasal conditions did not result in a decrease in DBP, ***neffy*** with rhinitis resulted in a slight suppression of DBP increase but less pronounced than what is observed following Epinephrine IM. This may be due to the impact of allergic mediators that are released systemically when rhinitis was induced. It is well documented that allergic rhinitis and nasal allergen challenges stimulate the immediate release of mediators that induce vasodilation. When such mediators are released into systemic circulation, the vasodilatory effects likely suppress increase of SBP and DBP.
- The suppressed DBP observed during rhinitis may be mitigating ***neffy***'s effect on SBP, however even during rhinitis, ***neffy***'s effect on SBP was still comparable to the effect following Epinephrine 0.3 and 0.5 mg IM without rhinitis.

CONCLUSION

In the present study, epinephrine concentrations following ***neffy*** with rhinitis appeared to occur faster than other treatments evaluated with decreased C_{max} relative to ***neffy*** under normal condition. However, the decreased C_{max} associated with rhinitis was still comparable to the C_{max} of Epinephrine 0.3 mg IM with normal conditions, which is well known to be efficacious. ***neffy*** with rhinitis resulted smaller increases in SBP, DBP, HR relative to ***neffy*** with normal nasal conditions, but still were comparable to the PD responses following Epinephrine 0.3 mg and 0.5 mg IM.

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