Pharmacokinetics and Pharmacodynamics Following Repeat Dosing of *neffy,* Epinephrine Nasal Spray, Versus Intramuscular Injection During Induced Allergic Rhinitis

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RATIONALE

- Epinephrine is the first-line treatment for severe allergic reactions, including anaphylaxis (Lieberman 2015, Shaker 2020, Muraro 2022). Delayed administration of epinephrine is associated with an increased risk of morbidity and mortality (Andrew 2018, Hochstadter 2016, Fleming 2015, Liu 2020, Turner 2017).
- ***neffy*** (epinephrine nasal spray) has been approved by FDA and EMA as the first needle-free option for intranasal epinephrine delivery. During ***neffy's*** development, pharmacokinetic and pharmacodynamic studies were conducted under a variety of conditions (Casale 2023a, Oppenheimer 2024, Casale 2023b, Sparapani 2024, Ellis 2024). The current study investigated repeated doses of ***neffy*** in patients with seasonal allergic reaction (SAR) following a nasal allergen challenge (NAC) to demonstrate that ***neffy*** will result in epinephrine exposure that is at least comparable to manual epinephrine injection by needle and syringe, which has been the basis for approval of all epinephrine auto-injectors.

METHODS

STUDY DESIGN AND PARTICIPANTS (Ellis 2015, Soliman 2018)

- Phase 1, five-treatment study, with two open-label randomized and cross-over treatment periods under normal condition followed by three open-label treatment periods under NAC, with at least 3 weeks wash-out period between NACs.
- Patients (n = 43, age 18 - 64) had confirmed seasonal allergies and positive NAC with Allergen Panel at Screening between 21 and 60 days prior to treatment. Subjects were required to have a Total Nasal Symptom Score (TNSS) of ≥5 out of 12 and a congestion score of ≥2 out of 3 on at least one test allergen during the screening NAC.
- Pharmacokinetic and pharmacodynamic assessments were done over 240 minutes.

BASELINE/OPEN-LABEL TREATMENT PERIODS (Figure 1)

Treatment Periods 1-2: Normal Nasal Conditions

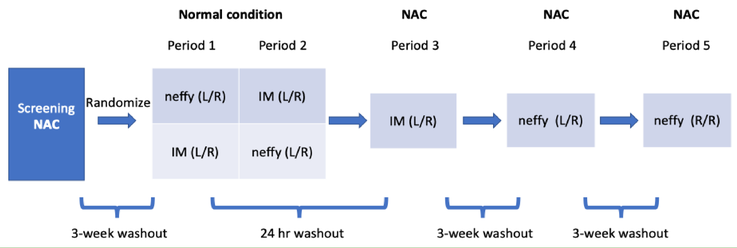
The PKs of two doses of ***neffy*** 2.0 mg were assessed and compared to two doses of IM 0.3 mg, all during normal nasal conditions. Two doses of ***neffy*** in the right and left naris administered 10 minutes apart; Two doses of IM 0.3 mg in the right and left anterolateral thigh administered 10 minutes apart.

Treatment Periods 3-5: Rhinitis

The PKs of two doses of ***neffy*** 2.0 mg were assessed and compared to two doses of IM 0.3 mg, all following the induction of rhinitis via NAC. The following treatments were administered, separated by a three-week wash-out period:

- Two doses of ***neffy*** 2.0 mg, both in the right naris administered 10 minutes apart;
- Two doses of ***neffy*** 2.0 mg in the right and left naris administered 10 minutes apart;
- Two doses of IM 0.3 mg in the right and left anterolateral thigh administered 10 minutes apart.

Figure 1: Study Design



RESULTS

This study included 43 patients (19 male and 24 female) with SAR, ages 24 to 63 years.

The baseline TNSSs before dosing were similar for the study periods. Average TNSS was 5.8 (±3.4) for Period 3, 6.1 (±3.3) for Period 4, and 6.3 (±3.1) for Period 5.

PHARMACOKINETIC RESULTS

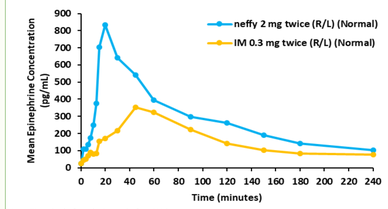
Normal Nasal Conditions

- Mean epinephrine concentrations under normal conditions were higher following ***neffy*** vs. IM; this difference persisted through the entire sampling period (240 minutes post-dose). Similarly, mean C_{max} values were also higher in ***neffy*** relative to IM (1064 vs. 420 pg/mL, p<0.001) and faster t_{max} (22 vs. 55 minutes, p<0.0001) (Figure 2).

NAC Conditions

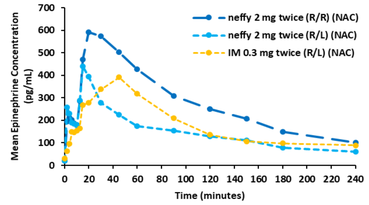
- When administered following NAC ***neffy*** (R/R) resulted in higher mean epinephrine concentrations relative to IM, also persisting through 240 minutes post-dose. ***neffy*** (R/L) also resulted in higher mean epinephrine concentrations relative to IM; however, the difference only persisted through 25 minutes post-dose (Figure 3).
- Mean C_{max} values were highest following ***neffy*** (R/R) (852 pg/mL) followed by ***neffy*** (R/L) (581 pg/mL) and IM (495 pg/mL) (p value vs. IM p<0.05, n.s.).

Figure 2: Mean Epinephrine Concentration versus Time Profiles, Normal Conditions



Note: Time 0 = before dosing or before NAC

Figure 3: Mean Epinephrine Concentration versus Time Profiles, NAC Conditions



Note: Time 0 = before dosing or before NAC

PHARMACODYNAMIC RESULTS

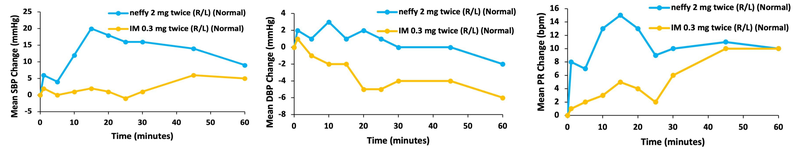
Normal Nasal Conditions

- The mean changes in SBP, DBP, and PR were greater following ***neffy*** relative to IM, with the differences in SBP and DBP persisting through 120 minutes post-dose and the difference in PR persisting through 60 minutes post-dose (Figure 4).
- All mean E_{max} values were significantly higher following ***neffy*** (SBP: 29 vs. 14 mmHg, p<0.001; DBP: 10 vs. 6 mmHg, p<0.001; PR: 24 vs. 14 mmHg, p<0.0001). Median T_{Emax} values for SBP and PR were faster following ***neffy***, with no significant difference noted for DBP (SBP: 19 vs. 38 mmHg, p<0.05; DBP: 15 vs. 10 mmHg, n.s.; PR: 16 vs. 45 mmHg, p<0.001).

NAC Conditions

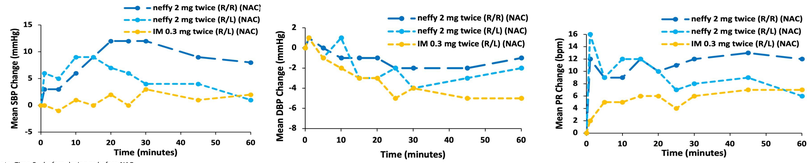
- The mean changes in SBP, DBP, and PR were greater following ***neffy*** (R/R) relative to IM, with the differences in all measures persisting through 120 minutes post-dose (Figure 5). The mean changes in SBP, DBP, and PR following ***neffy*** (R/L) were mostly greater than those of IM through 120 minutes post-dose (Figure 5).
- When ***neffy*** was administered (R/R), mean E_{max} values for SBP and PR were significantly higher relative to IM (SBP: 21 vs. 13 mmHg, p<0.01; PR: 22 vs. 14 mmHg, p<0.001). No significant differences were noted for DBP (DBP: 7 vs. 6 mmHg, n.s.). Median T_{Emax} values were also faster following ***neffy*** (R/R) (SBP: 26 vs. 30 mmHg, n.s.; DBP: 20 vs. 13 mmHg, n.s.; PR: 16 vs. 28 mmHg, p<0.01).
- When ***neffy*** was administered (R/L), mean E_{max} values were significantly higher for SBP and PR (SBP: 18 vs. 13 mmHg, p<0.05; PR: 22 vs. 14 mmHg, p<0.01). No significant differences were noted for DBP (DBP: 6 vs. 6 mmHg, n.s.). Median T_{Emax} values were also faster following ***neffy*** (R/L) (SBP: 16 vs. 30 mmHg, p<0.05; DBP: 10 vs. 13 mmHg, n.s.; PR: 11 vs. 28 mmHg, p<0.01).

Figure 4: Mean Change from Baseline SBP, DBP, and PR Versus Time Profiles, Normal Conditions



Note: Time 0 = before dosing or before NAC

Figure 5: Mean Change from Baseline SBP, DBP, and PR Versus Time Profiles, NAC Conditions



Note: Time 0 = before dosing or before NAC

SAFETY RESULTS

All adverse events were mild in severity and there were no serious adverse events. Regardless of nasal condition the most common events following ***neffy*** were throat irritation and nasal discomfort. Under normal conditions, throat irritation was reported by 14 subjects (32.6%) and nasal discomfort was reported by nine subjects (20.9%) Under NAC conditions, throat irritation was reported by one subject each for R/R and R/L administration (2.5% and 2.4%, respectively), and nasal discomfort was reported by five subjects (12.5%) following R/L and four subjects (9.8%) following R/R administration.

CONCLUSIONS

- Following twice dosing under SAR conditions, ***neffy's*** pharmacokinetic and pharmacodynamic profiles were comparable to or better than IM regardless of naris delivery method.
- These findings are consistent with what has been observed under normal condition and once dosing under NAC conditions.
- The data suggest that ***neffy*** will be a safe and effective treatment option for patients with allergic rhinitis who require a second dose of epinephrine to achieve full resolution of severe allergic reactions, including anaphylaxis.

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