ARS-1 (*neffy*® Nasal Spray) and Intramuscular Injection: Pharmacokinetic/Pharmacodynamic Differences and Differential Affinities for Adrenergic Receptors

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RATIONALE

- Epinephrine auto-injectors (EAIs) were initially approved based on the assumption that their pharmacokinetic and pharmacodynamic profiles were comparable to epinephrine delivery via manual injection via needle and syringe. A European Medicines Agency (EMA) request to generate pharmacokinetic data for autoinjector devices revealed that there are significant product-related differences in the pharmacokinetics (PK) and pharmacodynamics (PD) of approved EAIs.[1, 2, 3, 4, 5] Subsequent reports have confirmed that the pharmacokinetic profiles of these products cannot be considered interchangeable.[1] Comparative pharmacodynamic data is even more limited and it is not yet known how these pharmacokinetic differences translate into pharmacodynamic responses. Despite significant differences in pharmacokinetics, there is no evidence that any injection device results in differences in efficacy.
- ***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 clinical benefits by reducing apprehension and delay in dosing, reducing dosing errors, and making it easier to carry the product at all times. ***neffy*** is anticipated to have PK, PD, and safety profiles that are similar to currently approved epinephrine injection products but eliminates some needle related safety risks including blood vessel injections and accidental injection into an extremity (hand) by either the patient or caregiver.
- This analysis was conducted to compare the PK/PD relationship of epinephrine delivered via manual IM injection, EAIs (EpiPen®) and Symjepi®, and ***neffy***. Potential physiological mechanisms underlying the PD and PK/PD differences are also explored.

METHODS

- An integrated analysis (n = 175) was performed using data from four randomized, crossover, open-label, single-dose phase 1 trials. Two studies enrolled healthy individuals and two studies enrolled healthy volunteers with a history of type I allergies (allergic rhinitis, food allergy, venom allergy).
- The integrated analysis compared the PK and PD profiles of single and repeated doses of ***neffy*** (1.0 mg), EpiPen (0.3 mg), and manual IM injection via needle and syringe (0.3 mg). Single doses of Symjepi® (0.3 mg) and manual IM injection via needle and syringe (0.5 mg) were also included. All injections were administered to the anterolateral thigh per label. For repeated dose groups ***neffy*** was administered to opposite nares (L/R) or the same nare (L/L).
- Pharmacodynamic measurements were assessed as biomarkers of epinephrine efficacy, including change from baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were assessed before dosing and at various timepoints up to 120 minutes after dosing. All PD data are presented with the corresponding PK data (PK/PD relationship).

ANALYSIS POPULATION

A total of 175 subjects were included in the integrated analysis, with baseline demographics balanced between groups. The number of subjects dosed/group were as follows: ARS-1 1.0 mg (135), EpiPen (71), Symjepi (36), Epinephrine IM 0.3 mg (104), ARS-1 1.0 mg twice L/R (35), ARS-1 1.0 mg twice L/L (7), EpiPen twice (36), Epinephrine IM 0.3 mg twice (70), and Epinephrine IM 0.5 mg (92)

RESULTS

DOUBLE Y PLOTS

Double Y plots (by treatment) with epinephrine concentration (left axis) and PD response (right axis) versus time are presented in **Figure 1**.

PHARMACOKINETICS: The highest peak plasma concentration vs. time was observed following EpiPen®, followed by Symjepi® 0.3 mg, ***neffy*** 1.0 mg, and Epinephrine 0.3 mg IM.

PHARMACODYNAMICS: ***neffy*** 1.0 mg, EpiPen® 0.3 mg, and Symjepi® 0.3 mg resulted comparable increases in SBP and HR except HR following Symjepi® 0.3 mg, while smaller increases were observed following Epinephrine 0.3 mg IM. The increase in DBP was more pronounced following ***neffy*** 1.0 mg relative to injection products.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP: Regardless of treatment, SBP and HR began to increase immediately after administration of epinephrine, with the increases appearing to correlate with the mean concentration (**Figure 1**).

- **SBP**: Across all treatments, the mean change from baseline SBP appears to correlate with the mean epinephrine concentration (**Figure 1a**). However, when the graphs are compared by treatment, the mean concentration and mean SBP curves are close to each other following injections and spaced farther apart following ***neffy*** 1.0 mg. This spacing demonstrates that ***neffy*** 1.0 mg results in comparable increases in SBP at lower epinephrine concentrations relative to injections.
- **DBP**: While there was an inverse relationship between epinephrine concentration and DBP change for all treatments, ***neffy*** resulted in an increase in DBP during the first 30-minutes post-dose (**Figure 1b**). The degree of DBP decrease was similar among the injection products, while the decrease following ***neffy*** was less pronounced.
- **HR**: Across all treatments, the mean change from baseline HR also appears to correlate with the mean epinephrine concentration (**Figure 1c**). The change from baseline HR and epinephrine curves following EpiPen® 0.3 mg and Symjepi® 0.3 mg are closer to each other and spaced further apart following ***neffy*** 1.0 mg and Epinephrine 0.3 mg IM, again suggesting that ***neffy*** 1.0 mg and Epinephrine 0.3 mg IM produce comparable increases in HR at lower epinephrine concentrations relative to injection.

CORRELATION BETWEEN PD EFFECT AND EPINEPHRINE CONCENTRATION AS A FUNCTION OF TIME

The graphical finding of the correlation between the PD effect and epinephrine concentration by timepoint is presented in **Figure 2**. In general, the figures show clockwise hysteresis, suggesting that measured effect decreases with time for given epinephrine concentration. **Figure 2** also demonstrates ***neffy***'s ability to elicit comparable PD responses at lower epinephrine concentrations relative to injection.

- **SBP**: In the SBP vs. concentration figures, ***neffy*** 1.0 mg, EpiPen® 0.3 mg and Symjepi® 0.3 mg appear to have similar loop within lower concentration following ***neffy*** 1.0 mg whereas the loop following Epinephrine 0.3 mg IM is notably smaller.
- **DBP**: In the DBP vs. concentration figures, the loop with ***neffy*** 1.0 mg is mostly above baseline whereas the loops of injections are below baseline. The loop of Epinephrine 0.3 mg IM appears almost no hysteresis compared to other treatments.
- **HR**: In the HR vs. concentration figures, For HR, ***neffy*** 1.0 mg has almost no hysteresis, suggesting that epinephrine concentrations correlate closely with the HR.

MAXIMUM PD EFFECT (E_{max}) VS MAXIMUM EPINEPHRINE CONCENTRATION (C_{max})

Figure 3 demonstrates that there is a ceiling effect for all treatments, whereby additional increase in concentration do not translate into continued increases in SBP, DPB, or PR. ***neffy***'s relative efficiency is also demonstrated by **Figure 3**, with peak SBP and HR responses (E_{max}) being observed at lower C_{max} relative to injection.

DISCUSSION/CONCLUSION

- ***neffy*** increases SBP and HR more efficiently than injections, eliciting a comparable PD response at a lower epinephrine concentration.
- The more efficient increase in SBP following intranasal ***neffy*** administration relative to injections may be attributed to its bypassing of the β2-receptors in skeletal muscle.
  - β2 adrenergic receptors are found in the skeletal muscle and have a relatively high affinity for epinephrine, resulting in early activation, immediately post-dose, before epinephrine levels peak. β2-receptor activation results in vasodilation in the skeletal muscle, causing a decrease in peripheral vascular resistance and increased blood flow to skeletal muscle, ultimately resulting in a decrease in DBP.
  - This decrease in DBP may delay the increase in SBP, which is mediated by the lower affinity α1 receptors.
  - ***neffy's*** IN administration bypasses the β2-receptors in skeletal muscle and may allow for a more efficient increase both DBP and SBP.
- This increase efficiency may also be related to ***neffy's*** ability to increase HR without stimulating compensatory responses.
- IM injection results in a sudden increase in both SBP and HR which may stimulate compensatory responses and suppresses further increases in HR
- The suppressed HR then mitigates both the inotropic and chronotropic responses, which, in turn, suppress the SPB response.
- Scatter plots of mean SBP change versus epinephrine concentration (**Figure 3**) demonstrate that the maximum increase in SBP occurs at a plasma concentration of approximately 1000 pg/mL, and that further increase in plasma epinephrine levels do not translate into additional increases in SBP.

Figure 1: Double Y Plots -- Epinephrine Concentration (left axis) and PD Response (right axis) vs. Time

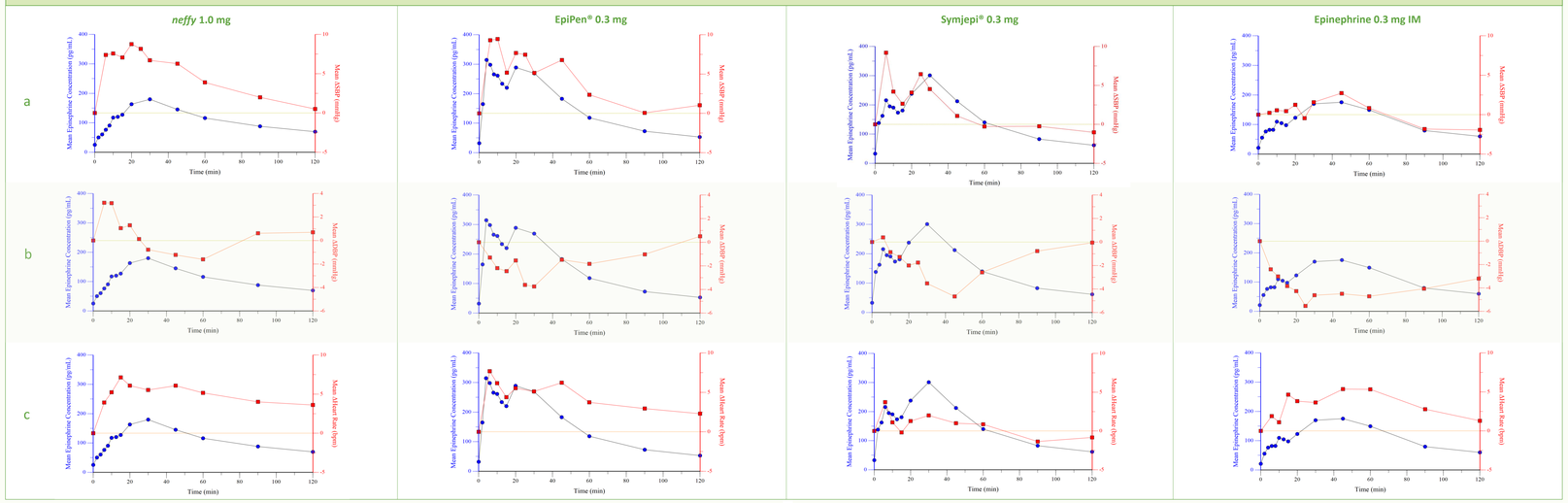


Figure 2: Correlation Between PD Effect and Epinephrine Concentration by Timepoint (Hysteresis Plots)

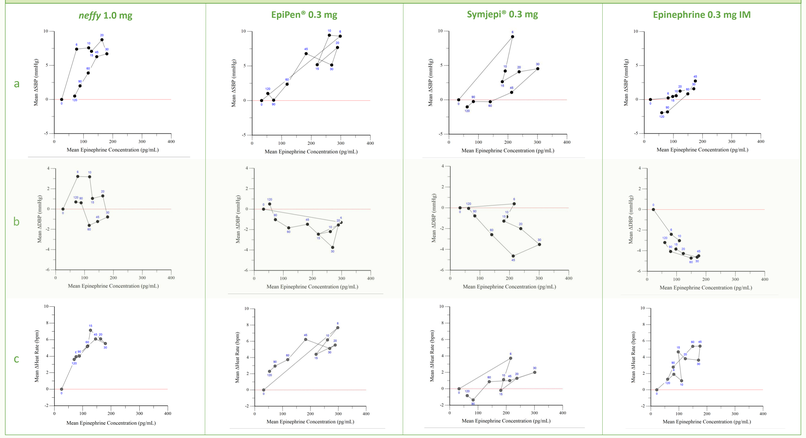
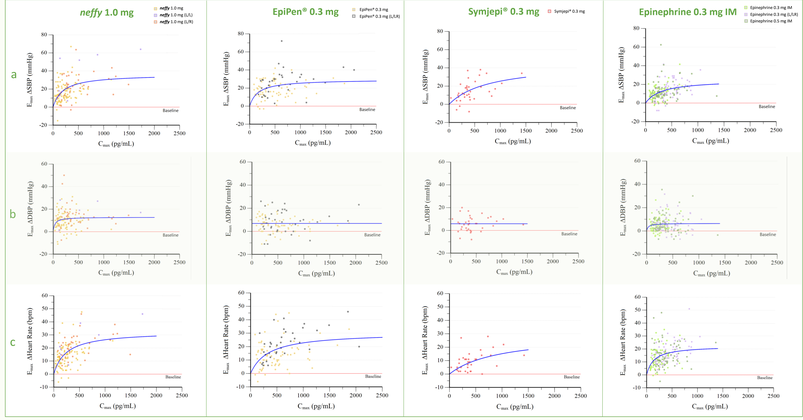


Figure 3: Relationship Between Maximum PD Effect (E_{max}) and Maximum Epinephrine Concentration (C_{max})



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