Pharmacokinetics/Pharmacodynamics of Intranasal Epinephrine in Subjects with and without Upper Respiratory Infections

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RATIONALE

- Epinephrine autoinjectors (EAIs) are the first line therapy for out-of-hospital treatment of severe allergic reactions, including anaphylaxis. Up to 83% of patients/caregivers fail to administer treatment or delay the use of EAIs even when they know a severe allergic reaction is occurring.[1-5]
- Barriers to the use of EAIs include high costs, safety concerns, failure to carry, failure to recognize a reaction, and lack of proper training on how to use the device.[6,7,8]
- A needle-free epinephrine delivery device is expected to have significant clinical benefit to patients by reducing treatment apprehension and delay, reducing dosing errors, and making it easier to always carry the product.
- ***neffy***®, an intranasal (IN) epinephrine spray is being developed for the emergency treatment of (Type I) allergic reactions, including anaphylaxis.
- To understand the impact of nasal edema and congestion on the absorption of epinephrine administered via ***neffy***, this study was conducted to evaluate pharmacokinetics (PK) and pharmacodynamics (PD) properties of ***neffy*** in subjects with and without upper respiratory tract infections (URTI).

METHODS

This was a Phase 1, single-dose, two-period study in subjects who were enrolled when they experienced an URTI with nasal congestion and edema (e.g., flu, common cold, nasal infection).

This study was approved by the Advarra IRB (US)/Human Research Ethics Committee and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All subjects provided written informed consent prior to screening.

Subjects received the following sequential treatments:

- 2.0 mg ***neffy*** in the left nostril, when experiencing an URTI with edema and congestion
- 2.0 mg ***neffy*** in the right nostril, under normal nasal conditions

The first treatment was with an URTI. After treatment, subjects were discharged and instructed to return after they recovered from the underlying illness. Upon return, subjects received a second dose under normal nasal conditions.

Table 1: Study Participants

Age (range)	Males	Females	Height mean (SD)	Weight mean (SD)	Body Mass Index mean (SD)
19-55 Years Old	11 (52.0%)	10 (48.0%)	169.0 (10.4) cm	78.0 (13.1) kg	27.2 (3.6) kg/m^2

A total of 21 subjects were enrolled, with 16 (76.2%) subjects completing the study. All 21 subjects received at least one dose of study medication. Five subjects withdrew prematurely (one due to withdrawal by subject, two due to physician decision , and two were lost to follow-up).

RESULTS

PHARMACOKINETIC RESULTS (Figures 1, 2 & Table 2)

For the first 25 minutes post-dose, the URTI did not appear to have any meaningful effect on epinephrine absorption.

There were no statistically significant differences in PK parameters. Mean peak plasma concentrations (C_{max}) were 490 pg/mL during the URTI and 570 pg/mL during normal nasal conditions. Total exposure (mean AUC_{0-t}) was 58,700 min*pg/mL during the URTI and 64,400 min*pg/mL during normal nasal conditions. The time to reach C_{max} (t_{max}) was 45.0 minutes during the URTI and 45.7 minutes during normal nasal conditions.

PHARMACODYNAMIC RESULTS (Figure 3)

The presence of an URTI did not have a significant impact on the pharmacodynamic response (including SBP and HR) to ***neffy*** 2.0 mg.

The pharmacodynamic responses observed under URTI conditions in this study are consistent with the observed and expected responses to ***neffy*** 2.0 mg in other clinical studies.

SAFETY RESULTS

The study treatments were well tolerated, with only mild or moderate treatment emergent adverse event (TEAEs) being reported. Most subjects had no post-dose nasal symptoms; when nasal symptoms were observed they were categorized as mild.

CONCLUSIONS

During the critical first 25 minutes post-dose, URTI did not appear to have any meaningful effect on epinephrine absorption or on the expected pharmacodynamic responses. Based on these data, ***neffy*** provides efficacious exposures under the theoretical worst-case Nasal Allergen Challenge induced nasal rhinitis, even under conditions of nasal congestion and edema caused by a cold, flu, sinus infection or other viral infections. The slight increase in absorption observed in the first 10-15 minutes post-dose may be related to minor increase in vascular permeability due to expected inflammatory and immune responses, however, larger studies are needed.

Table 2: Mean Peak Plasma Concentration (Cmax)/Total Exposure (Mean AUC 0-t)

Treatment	N	T_{max} (min) Median (Range)	C_{max} (pg/mL) (CV%)	Mean AUC_{last} (min*pg / mL) (CV%)
neffy 2 mg URTI	21	45 (2 – 150)	490 (67%)	58,700 (61%)
neffy 2 mg normal	16	46 (10 – 150)	570 (56%)	64,400 (53%)

Upper respiratory tract infections did not have a meaningful effect on *neffy*'s pharmacokinetics or pharmacodynamics

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Figure 1: Mean (SE) Epinephrine Concentration- Time Profile, by Nasal Condition (240- and 60-) Minutes Scales

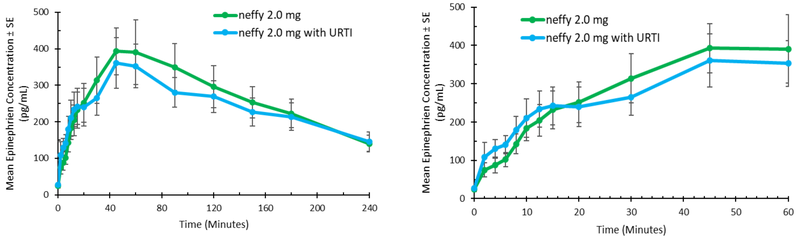


Figure 2: Ratio of Cmax and pAUCs by Nasal Condition (Test: URTI Condition and Reference: Normal Condition)

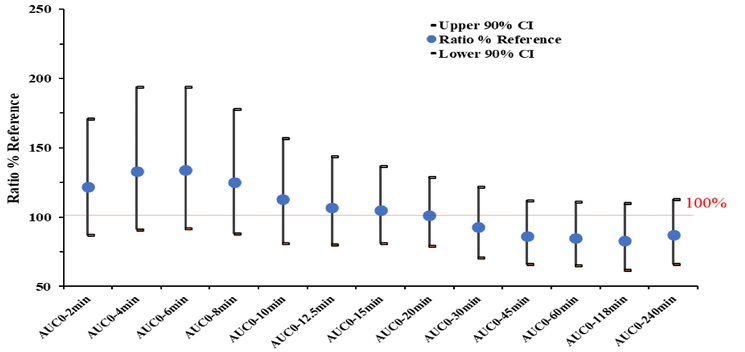
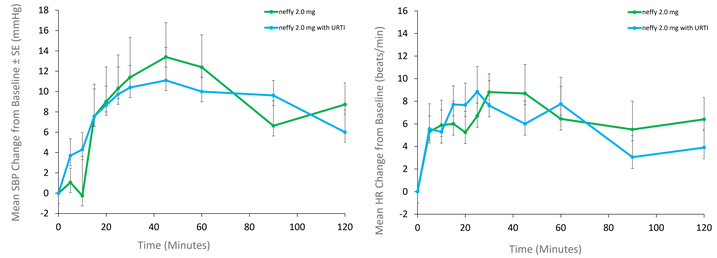


Figure 3: Pharmacodynamic Response to neffy, by Condition



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