Poster #036

Pharmacokinetic Profile of Epinephrine Nasal Spray Versus Intramuscular Epinephrine Autoinjector in Healthy Adults

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INTRODUCTION

- Anaphylaxis is a serious allergic reaction to food, insect stings, medications, and other allergens that requires immediate attention to avoid morbidity and potentially even death[1]
- First-line treatment for anaphylaxis is epinephrine, typically administered by an intramuscular (IM) autoinjector[2]
- Patients at higher risk of anaphylaxis are often prescribed epinephrine IM autoinjectors for self-administration, but their use can be hindered by a patient's fear of needles and injection injuries[3,4]
  - The patient's fear may result in a delay in administration or lack of use
- An epinephrine nasal spray (ENS; NDS1C, Bryn Pharma, Lebanon, NJ) is under development for the treatment of anaphylaxis that may increase the likelihood of self-administration compared with an autoinjector[5]
- Studies have shown that a single 13.2 mg ENS dose has higher and more sustained pharmacokinetic (PK) parameters compared with a 0.3 mg epinephrine dose administered via an IM autoinjector[6-8]

OBJECTIVE

- To compare the PK profile of 13.2 mg ENS with that of the standard of care 0.3 mg IM epinephrine autoinjector using pooled data from 4 studies

METHODS

Study design

- Data from 4 open-label phase 1 crossover studies were pooled for PK analysis[6,9-11]
- Participants in all 4 studies were healthy adults
- Treatment arms:
  - Single 13.2 mg ENS dose delivered by 2 consecutive sprays of 6.6 mg each in **opposite nostrils** (n=198)
  - Single 13.2 mg ENS dose delivered by 2 consecutive sprays of 6.6 mg each in the **same nostril** (n=74)
  - Single 0.3 mg epinephrine dose delivered by IM autoinjector (n=196)
- The consecutive intranasal sprays were administered within no more than 10 seconds of each other
- In all studies, each subject served as their own control per the crossover designs, with a washout period of at least 1 day between ENS and IM autoinjector treatment periods and of at least 14 days between the 2 ENS treatment periods
- All treatments were administered by trained clinical personnel

PK analysis

- Blood samples were collected to measure plasma epinephrine concentrations at –30, –20, and –10 minutes predose and 1, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, and 360 minutes postdose
- PK parameters included the maximum observed concentration (C_{max}), C_{max} from time 0 to 20 minutes (C_{max20}), time to reach C_{max} (T_{max}), and area under the plasma concentration–time curve (AUC) from time 0 to the 10-, 20-, 30-, 60-, and 360-minute postdose timepoints (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, AUC_{0-60}, and AUC_{0-360})

Statistical analysis

- Summary statistics for PK parameters were calculated by treatment and time point
- An analysis of variance (ANOVA) was performed on the baseline-adjusted natural log-transformed AUC and C_{max} plasma epinephrine parameters for each treatment
  - Test-to-reference ratios of least-squares means (LSM) and corresponding 90% confidence intervals (CIs) were calculated using the exponentiation of the difference between test and reference LSM and expressed as a percentage relative to the reference

Conclusions

- The 13.2 mg ENS dose delivered in opposite nostrils or the same nostril rapidly achieved therapeutic levels of epinephrine that were maintained for longer than the 0.3 mg IM autoinjector

RESULTS

- In the pooled population, 53% were male and the mean age was 39 years
- Epinephrine exposure was greater after 13.2 mg ENS than 0.3 mg IM autoinjector (**Figure 1**)
  - 13.2 mg ENS resulted in a rapid increase in plasma epinephrine concentration (**Figure 2**)
- The proportion of participants attaining specific concentration thresholds of 50, 100, and 200 pg/mL at 10-60 minutes postdose was similar across all treatments (**Figure 3**)
- The baseline-adjusted geometric means for AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, and AUC_{0-60} were similar between the 13.2 mg ENS and 0.3 mg IM autoinjector groups (**Table 1** and **Table 2**)
- The baseline-adjusted geometric mean for AUC_{0-360} was higher with 13.2 mg ENS than with 0.3 mg IM autoinjector, with a geometric mean ratio of 155% with 13.2 mg ENS in opposite nostrils and 159% with 13.2 mg ENS in the same nostril compared with 0.3 mg IM autoinjector (**Table 1** and **Table 2**)
- The median (range) T_{max} (minutes) with 13.2 mg ENS in opposite nostrils, 13.2 mg ENS in the same nostril, and 0.3 mg IM autoinjector was 25.1 (1.3, 362.1), 20.1 (3.0, 120.2), and 20.0 (1.0, 121.3), respectively (**Table 1**)
- The rate of absorption was comparable between groups

Table 1. Baseline-adjusted plasma epinephrine PK outcomes

PK Parameter	13.2 mg ENS in Opposite Nostrils n=198	13.2 mg ENS in the Same Nostril n=74	0.3 mg IM Autoinjector n=196
AUC_{0-10}, pg*min/mL, geometric mean (CV%)	603 (326)	861 (166)	942 (155)
AUC_{0-20}, pg*min/mL, geometric mean (CV%)	2,002 (186)	2,741 (109)	2,370 (104)
AUC_{0-30}, pg*min/mL, geometric mean (CV%)	3,879 (134)	4,856 (97)	4,072 (83)
AUC_{0-60}, pg*min/mL, geometric mean (CV%)	8,953 (115)	10,240 (84)	8,217 (65)
AUC_{0-360}, pg*min/mL, geometric mean (CV%)	27,130 (92)	27,710 (75)	17,480 (52)
$C_{max0-20}$, pg/mL, geometric mean (CV%)	191.4 (151.9)	257.3 (99.6)	226.9 (103.3)
C_{max}, pg/mL, geometric mean (CV%)	262.8 (114.4)	332.0 (82.0)	285.7 (76.4)
T_{max}, min, median (minimum, maximum)	25.1 (1.3, 362.1)	20.1 (3.0, 120.2)	20.0 (1.0, 121.3)

AUC_{0-x}, area under the curve from 0 to x minutes postdose; C_{max}, maximum observed concentration; C_{max20}, maximum observed concentration from 0 to 20 minutes; CV, coefficient of variation; ENS, epinephrine nasal spray; IM, intramuscular; T_{max}, time to reach maximum concentration.

Table 2. Comparison of baseline-adjusted plasma epinephrine PK parameters

PK Parameter	13.2 mg ENS in Opposite Nostrils n=198 Geometric LSM	0.3 mg IM Autoinjector n=196 Geometric LSM	Geometric Mean Ratio, %	90% CI	Intrasubject CV%
AUC_{0-10}, pg*min/mL	603	942	64	51–80	216
AUC_{0-20}, pg*min/mL	2,002	2,370	85	71–100	133
AUC_{0-30}, pg*min/mL	3,879	4,072	95	83–110	103
AUC_{0-60}, pg*min/mL	8,953	8,217	109	97–123	82
AUC_{0-360}, pg*min/mL	27,130	17,480	155	140–172	66
C_{max}, pg/mL	262.8	285.7	92	81.3–104.0	86
	13.2 mg ENS in the Same Nostril n=74 Geometric LSM	**0.3 mg IM Autoinjector n=196 Geometric LSM**			
AUC_{0-10}, pg*min/mL	861	942	91	68–123	216
AUC_{0-20}, pg*min/mL	2,741	2,370	116	92–145	133
AUC_{0-30}, pg*min/mL	4,856	4,072	119	98–144	103
AUC_{0-60}, pg*min/mL	10,240	8,217	125	106–146	82
AUC_{0-360}, pg*min/mL	27,710	17,480	159	138–182	66
C_{max}, pg/mL	332.0	285.7	116.2	98.3–137.2	85.6

AUC_{0-x}, area under the curve from 0 to x minutes postdose; C_{max}, maximum observed concentration; CV, coefficient of variation; ENS, epinephrine nasal spray; IM, intramuscular; LSM, least-squares means.

Figure 1. Median baseline-adjusted plasma epinephrine concentration – time profiles from 0-360 minutes

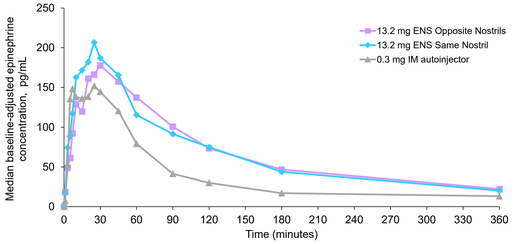


Figure 2. Median baseline-adjusted plasma epinephrine concentration – time profiles from 0-30 minutes

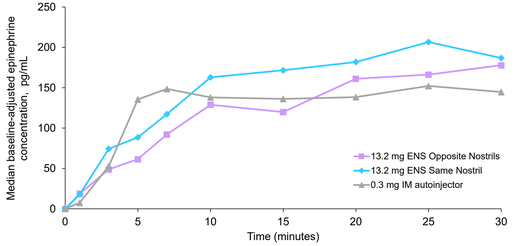
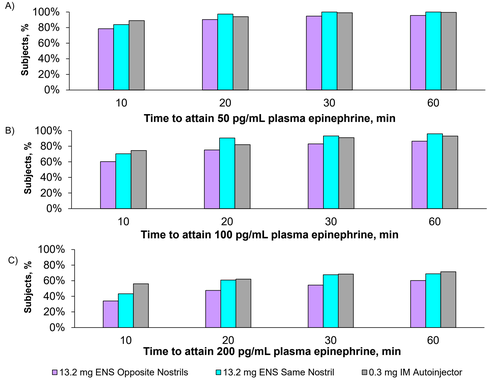


Figure 3. Proportion of participants attaining baseline-adjusted plasma epinephrine concentrations of A) 50 pg/mL, B) 100 pg/mL, and C) 200 pg/mL



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FUNDING AND DISCLOSURES: This research was supported by Bryn Pharma, LLC. Medical writing assistance was provided by Erin P. Scott, of Scott Medical Communications, LLC; funding for this assistance was provided by Bryn Pharma, LLC. M. Greenhawt is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, Bryn, Genentech, and Prota; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the Annals of Allergy, Asthma, and Immunology; and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, Red Nucleus, Medscape, Paradigm Medical Communications, Kaplan, and multiple state/local allergy societies