Poster # 8080

13.2 mg INTRANASAL EPINEPHRINE TREATMENT IN CONGESTION SHOWS INCREASED BIOAVAILABILITY WITHOUT PHARMACOKINETIC AND PHARMACODYNAMIC CORRELATION

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INTRODUCTION

- Epinephrine is the first-line treatment for anaphylaxis and is typically administered by an intramuscular (IM) autoinjector[1]
- Patients may delay using IM autoinjectors because they fear the pain or are anxious about using them correctly; delays in administration can increase the risk of hospitalization or potentially fatal outcomes[2-4]
- An epinephrine nasal spray (ENS) is under development as a mode of epinephrine administration for the treatment of anaphylaxis
- Nasal congestion (e.g., as a symptom of allergic rhinitis or anaphylaxis) could affect the absorption of an ENS
  - In pre-clinical studies, the 13.2 mg ENS dose demonstrated rapid absorption and overall exposure that increased with allergen-induced nasal congestion[5]

OBJECTIVES

- To compare the pharmacokinetics (PK) of 13.2 mg ENS with and without nasal congestion to IM treatments
- To explore the relationship of 13.2 mg ENS PK with pharmacodynamic (PD) effects and safety

METHODS

Study participants

- Healthy adults (19-65 y) with seasonal allergies
- Seasonal allergies were confirmed by clinical history and a positive skin prick test
- An adequate nasal congestive response to an allergen was confirmed by a total nasal symptom score ≥5/12, including a congestion score ≥2/3, during a nasal allergen challenge (NAC) conducted during screening

Study design

- Open-label, 4-period, 4-treatment, partial crossover study
- Participants were enrolled in either the opposite nostrils ENS cohort or the same nostril ENS cohort
- Both cohorts received the following treatments:
  - Period 1: 13.2 mg ENS (NDS1C; Bryn Pharma, Raleigh, NC) administered by 2 consecutive sprays, with congestion induced by NAC
  - Periods 2 and 3: 0.3 mg epinephrine by IM autoinjector or 0.5 mg epinephrine IM by manual syringe (MS) according to the randomization scheme
  - Period 4: 13.2 mg ENS administered by 2 consecutive sprays, without congestion
- There was a washout period of 1 day between Periods 1-3 and of at least 14 days between Periods 1 and 4
- All treatments were administered by trained clinical personnel

PK analysis

- Blood samples were collected to measure plasma epinephrine concentrations at −30, −20, −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})

PD analysis

- Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured at −30, −20, −10 minutes predose and 1, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, and 360 minutes postdose

Safety assessment

- Safety and tolerability were assessed by adverse event (AE) reporting

Statistical analysis

- Summary statistics for PK and PD parameters were calculated by cohort, 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 cohort
  - 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
  - Baseline-adjusted T_{max} was analyzed using nonparametric analysis for paired samples
- For HR and BP, an ANOVA was performed by cohort on the baseline-adjusted (change from baseline) maximum positive effect level (E_{max})
  - Test-to-reference ratios of LSM and corresponding 90% CIs were calculated using the ratio between test and reference LSM and expressed as a percentage relative to the reference
- ANOVA for PK and PD parameters was performed using sequence and treatment as fixed effects, and the subject nested within sequence as a random effect
- An average of 3 predose measurements (e.g., plasma concentration, HR, and BP) were used for baseline adjustments for each subject in each period

RESULTS

Participants

- Overall, 51 participants were enrolled in the study and 50 completed the study
- In Cohort 1, 46% were female, 62% were White, and the mean age was 38.7 years; in Cohort 2, 52% were female, 60% were White, and the mean age was 39.3 years (**Table 1**)

Table 1. Participant demographic characteristics

Characteristic	Cohort 1 (Opposite Nostrils) N=26	Cohort 2 (Same Nostril) N=25
Female, n (%)	12 (46)	13 (52)
Age, mean (range), y	38.7 (22-63)	39.3 (20-58)
Race, n (%)		
American Indian/Alaska Native	0	1 (4)
Black/African American	6 (23)	9 (36)
White	16 (62)	15 (60)
White, Asian	1 (4)	0
White, Black	2 (8)	0
White, Black, American Indian/Alaska Native	1 (4)	0
Height, mean (SD), cm	172.3 (9.3)	170.6 (7.4)
Weight, mean (SD), kg	80.9 (12.5)	78.6 (10.2)

PK

- 13.2 mg ENS by opposite nostrils or the same nostril under NAC resulted in higher exposures and more rapid T_{max} vs IM treatments and 13.2 mg ENS without NAC (**Table 2; Figure 1**)
- The proportion of participants attaining specific concentration thresholds of 50, 100, and 200 pg/mL at 10-60 minutes postdose was similar across treatments (**Figure 2**)
- The geometric mean ratios (GMRs; 90% CI) for C_{max} and AUC_{0-360} with 13.2 mg ENS with NAC vs without NAC in opposite nostrils were 170% (123%-234%) and 116% (91%-149%), respectively, and in the same nostril were 174% (115-263) and 161% (117-220), respectively (**Table 3**)
  - The GMRs (90% CI) for C_{max} and AUC_{0-360} with 13.2 mg ENS with NAC in opposite nostrils vs IM autoinjector were 164% (119%-226%) and 201% (157%-258%), respectively, and with 13.2 mg ENS with NAC in the same nostril vs IM autoinjector were 191% (127-289) and 192% (140-263), respectively

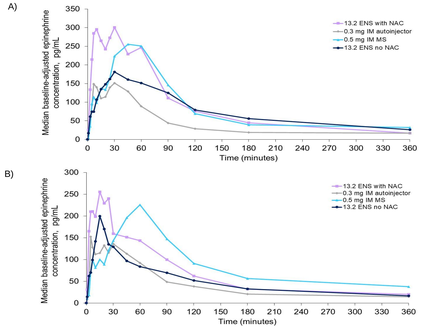
PD

- Postdose HR remained stable and relatively similar to predose values regardless of plasma epinephrine concentration (**Figure 3**)
- E_{max} unadjusted HR was ≤113 bpm for all treatments in either cohort
- The difference in E_{max} LSM values for change from baseline HR ranged from −6.1-1.1 among all treatment comparisons in Cohort 1, and from −5.8-5.0 in Cohort 2
- SBP and DBP remained stable and relatively similar to predose values regardless of plasma epinephrine concentration

Safety

- The treatment-emergent AE incidences with 13.2 mg ENS with and without NAC in opposite nostrils were 54% and 64%, respectively, and in the same nostril were 44% and 48%, respectively (**Table 4**)
- Mild nausea and headache were the most common AEs with 13.2 mg ENS treatment (**Table 4**)

Figure 1. Median baseline-adjusted plasma epinephrine concentration – time profiles after ENS with or without NAC or IM epinephrine in A) Cohort 1 (opposite nostrils) or B) Cohort 2 (same nostril).



RESULTS CONT.

Table 2. Baseline-adjusted plasma epinephrine PK outcomes after ENS with or without NAC or IM epinephrine

PK Parameter	Cohort 1 (Opposite Nostrils) N=26				Cohort 2 (Same Nostril) N=25			
	13.2 mg ENS with NAC	IM autoinjector	IM MS	13.2 mg ENS without NAC	13.2 mg ENS with NAC	IM autoinjector	IM MS	13.2 mg ENS without NAC
C_{max}, pg/mL, geometric mean (CV%)	458.0 (117.9)	279.0 (63.4)	364.2 (68.9)	270.1 (102.5)	436.3 (334.4)	228.2 (83.7)	322.3 (48.8)	250.8 (70.5)
C_{max20}, pg/mL, geometric mean (CV%)	399.3 (122.4)	219.3 (90.1)	170.6 (171.7)	203.7 (121.7)	367.1 (358.0)	182.0 (99.0)	131.2 (112.7)	224.0 (71.9)
T_{max}, min, median (minimum, maximum)	15 (3, 180)	21 (3, 91)	45 (1, 120)	25 (5, 120)	18 (3, 90)	20 (3, 45)	45 (5, 180)	20 (5, 120)
AUC_{0-10}, pg*min/mL, geometric mean (CV%)	1,681 (171)	799 (164)	555 (329)	686 (213)	1,431 (333)	808 (143)	432 (228)	628 (116)
AUC_{0-20}, pg*min/mL, geometric mean (CV%)	4,688 (135)	2,149 (97)	1,773 (184)	2,307 (129)	4,140 (295)	1,972 (117)	1,356 (123)	2,335 (70)
AUC_{0-30}, pg*min/mL, geometric mean (CV%)	7,472 (122)	3,781 (71)	3,560 (136)	4,266 (118)	6,760 (285)	3,353 (96)	2,737 (87)	3,942 (71)
AUC_{0-60}, pg*min/mL, geometric mean (CV%)	14,020 (123)	7,978 (48)	11,410 (63)	9,508 (102)	12,780 (255)	6,924 (87)	9,183 (48)	7,575 (68)
AUC_{0-360}, pg*min/mL, geometric mean (CV%)	34,200 (100)	16,710 (52)	32,400 (44)	29,680 (76)	33,970 (179)	18,090 (43)	32,260 (50)	21,440 (58)

AUC_{x-y}, 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; MS, manual syringe; NAC, nasal allergen challenge; T_{max}, time to reach maximum concentration.

Table 3. Comparison of baseline-adjusted plasma epinephrine PK parameters after ENS with or without NAC

PK Parameter	Cohort 1 (Opposite Nostrils) 13.2 ENS with NAC Geometric LSM	13.2 ENS without NAC Geometric LSM	GMR, %	90% CIs	Intrasubject CV%
C_{max}, pg/mL	458	270	170	123-234	78
AUC_{0-360}, min*pg/mL	34,200	29,500	116	91-149	57
	Cohort 2 (Same Nostril) 13.2 ENS with NAC Geometric LSM	13.2 ENS without NAC Geometric LSM	GMR, %	90% CIs	Intrasubject CV%
C_{max}, pg/mL	435	250	174	115-263	107
AUC_{0-360}, min*pg/mL	34,130	21,250	161	117-220	73

AUC_{0-360}, area under the curve from 0 to 360 minutes postdose; C_{max}, maximum observed concentration; CI, confidence interval; CV, coefficient of variation; ENS, epinephrine nasal spray; GMR, geometric mean ratio; LSM, least-squares mean; NAC, nasal allergen challenge.

Table 4. Treatment-emergent AEs occurring in ≥10% of participants receiving ENS with or without NAC or IM epinephrine

Subjects with TEAE, n (%)	Cohort 1 (Opposite Nostrils) N=26				Cohort 2 (Same Nostril) N=25			
	13.2 mg ENS with NAC	IM autoinjector	IM MS	13.2 mg ENS without NAC	13.2 mg ENS with NAC	IM autoinjector	IM MS	13.2 mg ENS without NAC
Any TEAE	14 (54)	4 (15)	7 (27)	16 (64)	11 (44)	4 (16)	5 (20)	12 (48)
Headache	6 (23)	0	1 (4)	4 (16)	9 (36)	0	3 (12)	8 (32)
Nausea	4 (15)	1 (4)	0	8 (32)	4 (16)	0	0	3 (12)
Oropharyngeal pain	4 (15)	1 (4)	0	1 (4)	1 (4)	0	0	0
Vomiting	3 (12)	0	0	6 (24)	4 (16)	0	0	1 (4)
Nasal discomfort	2 (8)	0	0	6 (24)	0	0	0	0
Upper abdominal pain	1 (4)	0	0	3 (12)	3 (12)	0	0	3 (12)
Injection site pain	0	3 (12)	3 (12)	0	0	1 (4)	1 (4)	0

AE, adverse event; ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge.

Figure 2. Proportion of participants attaining baseline-adjusted plasma epinephrine concentrations of A) 50 pg/mL, B) 100 pg/mL, and C) 200 pg/mL after ENS with or without NAC or IM epinephrine in Cohort 1 (opposite nostrils) or Cohort 2 (same nostril).

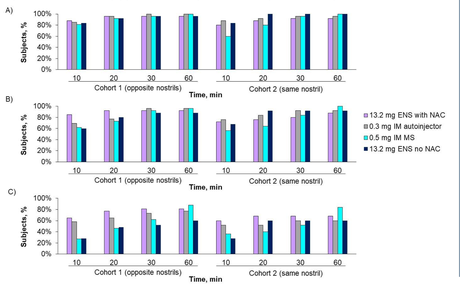
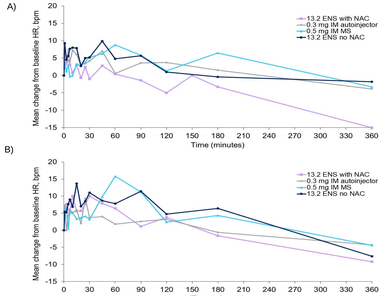


Figure 3. Mean change from baseline heart rate – time profiles after ENS with or without NAC or IM epinephrine in A) Cohort 1 (opposite nostrils) or B) Cohort 2 (same nostril).



Conclusions

1. **13.2 mg ENS in congestion demonstrated enhanced absorption vs IM treatments and 13.2 mg ENS without congestion**
2. **PD treatment effects on HR, SBP, and DBP were minimal with no correlation between PK concentration and PD effects**
3. **13.2 mg ENS appeared safe and well tolerated**

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REFERENCES: **1.** Lieberman P, et al. *Ann Allergy Asthma Immunol.* 2015;115(5):341-384. **2.** Gallagher M, et al. *Clin Exp Allergy.* 2011;41(6):869-877. **3.**Fleming JT, et al. *J Allergy Clin Immunol Pract.* 2015;3(1):57-62. **4.** Pumphrey RSH. *Clin Exp Allergy.* 2000;30(8):1144-1150. **5.** Data on file: Bryn Pharma; 2023.

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