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Randomized trial of pharmacokinetic and pharmacodynamic effects of 13.2 mg intranasal epinephrine treatment in congestion

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ABSTRACT

Background: Nasal congestion could affect the absorption of an epinephrine nasal spray (ENS).
Objective: To compare the pharmacokinetics of 13.2 mg ENS with nasal congestion vs without congestion and vs intramuscular (IM) treatments.
Methods: This phase I, open-label, 4-period randomized crossover study enrolled 51 healthy adults with seasonal allergies into cohorts that received a single dose of 13.2 mg ENS (NDS1C; Bryn Pharma, Lebanon, New Jersey) administered as 2 consecutive sprays in either opposite nostrils (cohort 1) or the same nostril (cohort 2). Both cohorts received 13.2 mg ENS with and without nasal allergen challenge (NAC), 0.3 mg IM epinephrine by autoinjector, and 0.5 mg IM epinephrine by manual syringe (MS).
Results: The ENS after NAC resulted in higher extent and peak exposures and more rapid time to maximum plasma concentration vs ENS without NAC and IM treatments. In cohort 1, the maximum observed baseline-adjusted epinephrine plasma concentration (pg/mL) of ENS with NAC, IM autoinjector, IM MS, or ENS without NAC was 458.0, 279.0, 364.2, and 270.1, respectively, and in cohort 2 was 436.3, 228.2, 322.3, and 250.8, respectively. The maximum observed baseline-adjusted epinephrine plasma concentration geometric mean ratio (90% CI) for ENS with NAC vs without NAC in cohort 1 was 170% (123%-234%), and in cohort 2 was 174% (115%-263%). In cohort 1, the time to maximum plasma concentration was 15, 21, 45, and 25 minutes, respectively, and in cohort 2 was 18, 20, 45, and 20 minutes, respectively ($P < .01$ for ENS with NAC vs IM MS). The postdose mean heart rate and blood pressure remained stable and relatively similar to predose values regardless of plasma epinephrine concentration. Mild nausea and headache were the most common adverse events with ENS.
Conclusion: The 13.2 mg ENS with congestion exhibited enhanced absorption vs IM treatments and ENS without congestion and seemed to be well tolerated. There was no clinically impactful relationship between pharmacodynamic effects and plasma epinephrine concentration.

Introduction

Anaphylaxis is a severe, potentially life-threatening systemic allergic reaction that can occur on exposure to medications, insect stings, food allergens, and other triggers. Intramuscular (IM) epinephrine is the first line of treatment for anaphylaxis and is typically administered by an autoinjector.[1,2] It can also be administered by means of a manual syringe (MS). Timely administration of epinephrine is critical because an anaphylactic event can become fatal within minutes after exposure to the culprit trigger.[1,2] Individuals who are at risk of experiencing an anaphylactic reaction, such as those with severe food allergies, may be prescribed IM autoinjectors to enable self-administration should they experience an anaphylactic reaction.[3] However, studies indicate that patients may delay using IM autoinjectors because they fear the pain or are anxious about using them correctly.[4,5] Unfortunately, such delays in administration can increase the risk of hospitalization or fatal outcomes.[6-8]

An epinephrine nasal spray (ENS) (NDS1C; Bryn Pharma, Lebanon, New Jersey) is under development as a mode of epinephrine administration for the treatment of anaphylaxis. There is a possibility that nasal congestion (eg, as a symptom of allergic rhinitis or anaphylaxis) could affect the absorption of an ENS. In preclinical studies conducted in beagle dogs, ENS exhibited rapid absorption and overall exposure that increased 2 to 3 times in a histamine nasal congestion model.[9] The current study was conducted in healthy adults to compare the pharmacokinetics (PK) of 13.2 mg ENS with nasal congestion to 13.2 mg ENS without nasal congestion and to IM treatments

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administered by autoinjector or MS. The study also explored the relationship of 13.2 mg ENS PK with pharmacodynamic (PD) effects and safety.

Methods

This was a phase I, open-label, randomized, 4-period, partial crossover study conducted from March 2022 through August 2022. The study was approved by the Advarra institutional review board before study initiation. Written informed consent was obtained from all participants. The study was conducted in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Nasal Allergen Challenge

A nasal allergen challenge (NAC) was conducted as part of the screening process to confirm an adequate nasal congestive response to intranasal allergen and to determine the qualifying allergen concentration to be used in period 1 for inducing nasal congestion. Periods 2, 3, and 4 did not have a NAC. An adequate nasal congestive response to an allergen at screening and in period 1 was defined as a total nasal symptom score (TNSS) greater than or equal to 5 out of a maximum of 12, including a congestion score greater than or equal to 2 out of a maximum of 3 on the basis of the US Food and Drug Administration Guidance for Industry.[10] The TNSS was the sum of the scores for rhinorrhea, nasal congestion, nasal itching, and sneezing each rated on a scale of 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), or 3 (severe symptoms). The qualifying allergen concentration that was determined to induce adequate nasal congestion during the screening NAC was delivered into a single nostril 30 minutes before administration of ENS in period 1. For same-nostril ENS dosing, both sprays were administered into the nostril that received the allergen challenge. The TNSS was obtained up to 5 minutes before ENS dosing in period 1 to ensure that each participant reached the protocol-defined adequate nasal congestive response and in period 4 to ensure they did not have nasal congestion.

Treatment

Participants were enrolled in either a cohort that received each single-dose administration of 13.2 mg ENS (a single dose is delivered as 2 consecutive sprays of 6.6 mg each) in opposite nostrils (cohort 1) or a cohort that received each single-dose administration of 13.2 mg ENS (delivered as 2 consecutive sprays of 6.6 mg each) in the same nostril (cohort 2). The consecutive sprays were administered within 10 seconds of each other. In each cohort, participants were randomized in a 1:1 ratio to 1 of 2 treatment sequences in 13 blocks of size 2. The randomization code was computer-generated by members of the Celerion Statistics Department. All participants in both cohorts received 13.2 mg ENS with congestion induced by NAC in period 1, 0.3 mg epinephrine by IM autoinjector (Mylan Specialty L.P., Morgantown, West Virginia) or 0.5 mg epinephrine IM by MS (PAR Pharmaceutical, Woodcliff Lake, New Jersey) according to the randomization scheme in periods 2 and 3, and 13.2 mg ENS without congestion, in period 4. There was a washout period of 1 day between periods 1, 2, and 3 and at least 14 days between periods 1 and 4. All treatments were administered by trained clinical personnel. The IM injections by autoinjector or MS were administered to the middle of the outer thigh.

Study Participants

Eligible participants were healthy, nonsmoking adults (aged 19-65 years) with a history of seasonal allergies for at least 2 years before screening and a body mass index of between 18.0 and 32.0 kg/m^2 at screening. Seasonal allergies were confirmed by clinical history and a positive skin prick test. Participants were required to have a TNSS less than 5 of the maximum score of 12, including a congestion score less than 2 of the maximum score of 3, before NAC at screening and in period 4 and reach an adequate nasal congestive response to an allergen after the NAC at screening and in period 1. Participants with any signs of a respiratory tract infection within 6 weeks of screening deemed clinically significant by the investigator, a history of extensive nasal or sinus surgery, or known nasal obstruction including nasal polyposis, severe mucosal swelling, nasal ulcers, or nasal trauma, were excluded from the study.

Assessments

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. The PK parameters included the maximum observed plasma concentration (C_{max}), C_{max} from time 0 to 20 minutes postdose (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 time points (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, AUC_{0-60}, and AUC_{0-360}). Plasma epinephrine concentrations were determined using a validated ultra-performance liquid chromatographic method with tandem mass spectrometry detection method.

Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured in a semireclined position 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.

Safety and tolerability were assessed by adverse event (AE) reporting and coded using the Medical Dictionary for Regulatory Activities, Version 25.0.

Outcomes

The primary objective was to compare the PK of a single dose of 13.2 mg ENS in healthy participants with seasonal allergies, with and without nasal congestion. Secondary objectives included a comparison of the PD effects (expressed as changes in HR and BP) and the safety and tolerability after a single dose of 13.2 mg ENS in healthy participants with seasonal allergies, with and without nasal congestion, and comparison of PK and PD between 13.2 mg ENS administration with and without nasal congestion and IM administration.

Statistical Analysis

A total of 50 participants were to be enrolled in the study, with 25 participants enrolled in each cohort. All participants who were enrolled in the study were included in the PK and PD analyses to the extent possible. Descriptive statistics for demographics were calculated for each cohort. Descriptive statistics for PK and PD parameters were calculated by cohort, treatment, and time point using Statistical Analysis System version 9.4 (SAS Institute, Cary, North Carolina). 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 mean (LSM) and corresponding 90% CIs were calculated using the exponentiation of the difference between test and reference LSM and expressed as a percentage relative to the reference. Statistical significance was indicated when the 90% CI did not cross 100%. Baseline-adjusted T_{max} was analyzed using nonparametric analysis for paired samples. Analysis of the proportions attaining specific epinephrine concentration thresholds was descriptive only.

For the HR, SBP, and DBP, ANOVA was performed by cohort on the maximum positive effect level (E_{max}) adjusted for baseline (change from baseline). 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.

The ANOVA for PK and PD parameters was performed using sequence and treatment as fixed effects, and the subject nested within the sequence as a random effect. An average of 3 predose measurements (eg, plasma concentration, HR, SBP, and DBP) were used for baseline adjustments for each participant in each period.

Results

Participants

Overall, 51 participants were enrolled in the study, and 50 completed the study. A total of 26 participants entered cohort 1 and were randomized to treatments; 25 participants completed the study, and 1 participant discontinued for personal reasons. A total of 25 participants entered cohort 2 and were randomized to treatments; 25 participants completed the study. In cohort 1, 46% were females, 62% identified as White, 23% identified as Black, and the mean age was 38.7 years; in cohort 2, 52% were females, 60% identified as White, 36% identified as Black, and the mean age was 39.3 years (Table 1).

Pharmacokinetics

Administration of 13.2 mg ENS either in opposite nostrils (cohort 1) or the same nostril (cohort 2) after NAC resulted in higher extent and peak exposures and more rapid T_{max} vs 13.2 mg ENS administered without NAC and IM treatments (Table 2; Fig 1A and B). In cohort 1, C_{max} (pg/mL) with 13.2 mg ENS with NAC, IM autoinjector, IM MS, or 13.2 mg ENS without NAC was 458.0, 279.0, 364.2, and 270.1, respectively, and in cohort 2 was 436.3, 228.2, 322.3, and 250.8, respectively (Table 2). In cohort 1, T_{max} was 15, 21, 45, and 25 minutes, respectively, and in cohort 2 was 18, 20, 45, and 20 minutes, respectively ($P < .01$ for 13.2 mg ENS with NAC vs IM by MS in cohort 1 and cohort 2; $P < .01$ for 13.2 mg ENS without NAC vs IM by MS in cohort 2 only [Table 2]). The proportion of participants attaining specific epinephrine concentration thresholds of 50, 100, and 200 pg/mL at 10 to 60 minutes postdose was similar across treatments, indicating that ENS administration achieved equivalent plasma concentrations as quickly as IM administration (Fig 2A, B, and C). On the basis of baseline-adjusted epinephrine data, the geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}360}$ with 13.2 mg ENS with NAC vs without NAC in cohort 1 were 170% (123%-234%) and 116% (91%-149%), respectively, and in cohort 2 were 174% (115%-263%) and 161% (117%-220%), respectively (Table 3). The geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}360}$ with 13.2 mg ENS with NAC in cohort 1 vs IM autoinjector were 164% (119%-226%) and 201% (157%-258%), respectively, and with 13.2 mg ENS with NAC in cohort 2 vs IM autoinjector were 191% (127%-289%) and 192% (140%-263%), respectively.

Pharmacodynamics

Postdose HR remained stable and relatively similar to predose values regardless of plasma epinephrine concentration (Fig 3A and B). Scatterplots of change from baseline HR vs time-matched baseline-adjusted plasma epinephrine concentrations resulted in an R^2 of 0.0396 in cohort 1 and an R^2 of 0.0141 in cohort 2. The E_{max} unadjusted HR was less than or equal to 113 beats per minute (bpm) for all treatments in either cohort. The difference in E_{max} LSM values for change from baseline HR among all treatment comparisons was nonsignificant and ranged from −6.1 to 1.1 bpm in cohort 1 and from −5.8 to 5.0 bpm in cohort 2 (eTable 1). The SBP and DBP remained stable and relatively similar to predose values regardless of plasma epinephrine concentration (Fig 4A and B; eFig 1A and B). Scatterplots of change from baseline SBP and DBP vs time-matched baseline-adjusted plasma epinephrine concentrations resulted in an R^2 less than or equal to 0.0227 for all comparisons. There were a few significant differences in E_{max} LSM values for change from baseline SBP and DBP between 13.2 mg ENS (with and without NAC) compared with IM administration, although the greatest difference was only 8.2 mmHg (90% CI, 1.7-14.6) for SBP and 5.7 mmHg (90% CI, 1.8-9.5) for DBP (eTable 1). None of the effects on HR or BP were clinically impactful.

Table 1
Participant Demographic Characteristics

Characteristics	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)
Body mass index, mean (SD), kg/m^2	27.2 (3.0)	27.0 (2.4)

Table 2
Baseline-Adjusted Plasma Epinephrine Pharmacokinetic Outcomes After Epinephrine Nasal Spray Administration With or Without Nasal Allergen Challenge or Intramuscular 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)[a]	25 (5, 120)	18 (3, 90)	20 (3, 45)	45 (5, 180)[a,b]	20 (5, 120)
$AUC_{0\text{-}10}$, pg × min/mL, geometric mean (CV%)	1681 (171)	799 (164)	555 (329)	686 (213)	1431 (333)	808 (143)	432 (228)	628 (116)
$AUC_{0\text{-}20}$, pg × min/mL, geometric mean (CV%)	4688 (135)	2149 (97)	1773 (184)	2307 (129)	4140 (295)	1972 (117)	1356 (123)	2335 (70)
$AUC_{0\text{-}30}$, pg × min/mL, geometric mean (CV%)	7472 (122)	3781 (71)	3560 (136)	4266 (118)	6760 (285)	3353 (96)	2737 (87)	3942 (71)
$AUC_{0\text{-}60}$, pg × min/mL, geometric mean (CV%)	14,020 (123)	7978 (48)	11,410 (63)	9508 (102)	12,780 (255)	6924 (87)	9183 (48)	7575 (68)
$AUC_{0\text{-}360}$, 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)

Abbreviations: $AUC_{0\text{-}x}$, area under the curve from 0 to X minutes postdose; C_{max}, maximum observed plasma concentration; C_{max20}, maximum observed plasma concentration from 0 to 20 minutes postdose; CV, coefficient of variation; ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge; PK, pharmacokinetic; T_{max}, time to reach maximum plasma concentration.

[a] *P* value less than .01 vs T_{max} of 13.2 ENS with NAC using nonparametric Wilcoxon signed rank test.

[b] *P* value less than .01 vs T_{max} of 13.2 ENS without NAC using nonparametric Wilcoxon signed rank test.

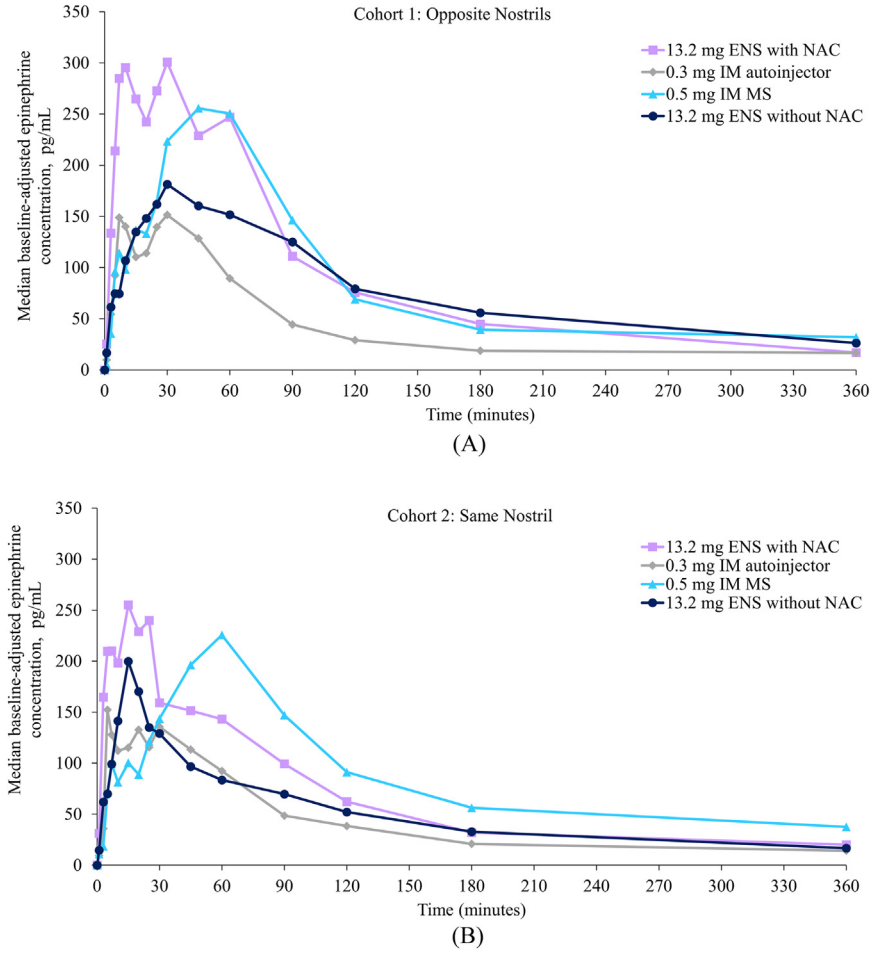

Figure 1. Median baseline-adjusted plasma epinephrine concentration-time profiles after ENS administration with or without NAC or IM epinephrine administration in (A) cohort 1 (opposite nostrils) or (B) cohort 2 (same nostril). ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge.

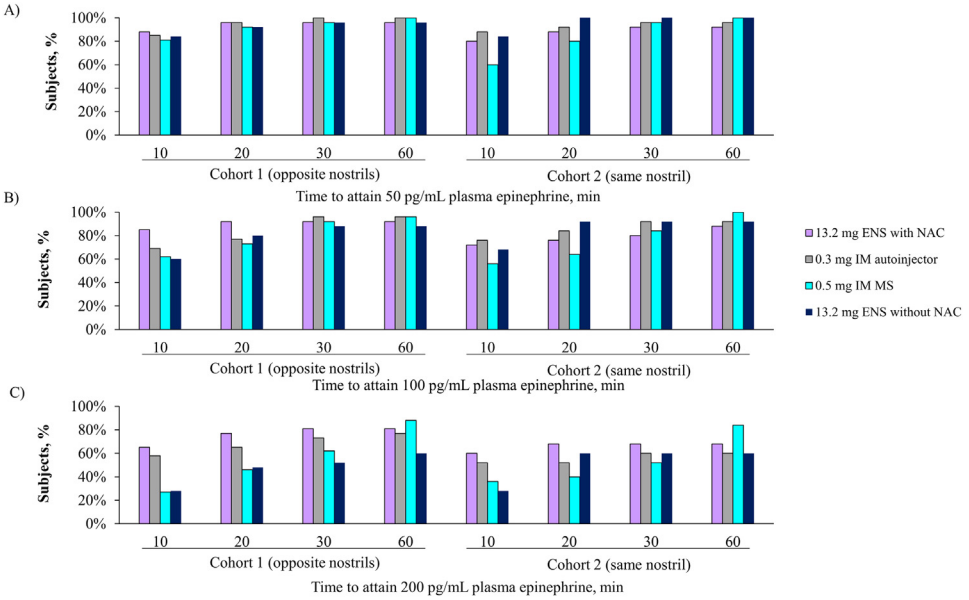

Figure 2. The proportion of participants attaining baseline-adjusted plasma epinephrine concentrations of (A) 50 pg/mL, (B) 100 pg/mL, and (C) 200 pg/mL after ENS administration with or without NAC or IM epinephrine administration in cohort 1 (opposite nostrils) or cohort 2 (same nostril). ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge.

Table 3
Comparison of Baseline-Adjusted Plasma Epinephrine Pharmacokinetic Parameters After Epinephrine Nasal Spray Administration With or Without Nasal Allergen Challenge

PK parameter	Cohort 1 (opposite nostrils)				
	13.2 mg ENS with NAC Geometric LSM	13.2 mg ENS without NAC Geometric LSM	GMR, %	90% CIs	Intrasubject CV%
C_{max}, pg/mL	458.0	270.1	170	123-234	78
AUC_{0-10}, min × pg/mL	1681	681	247	135-450	205
AUC_{0-20}, min × pg/mL	4688	2296	204	131-319	122
AUC_{0-30}, min × pg/mL	7472	4243	176	121-257	96
AUC_{0-60}, min × pg/mL	14,020	9471	148	111-198	69
AUC_{0-360}, min × pg/mL	34,200	29,500	116	91-149	57
PK parameter	Cohort 2 (same nostril)				
	13.2 mg ENS with NAC Geometric LSM	13.2 mg ENS without NAC Geometric LSM	GMR, %	90% CIs	Intrasubject CV%
C_{max}, pg/mL	435.0	250.0	174	115-263	107
AUC_{0-10}, min × pg/mL	1423	624	228	142-365	131
AUC_{0-20}, min × pg/mL	4121	2324	177	117-269	109
AUC_{0-30}, min × pg/mL	6731	3924	172	116-254	100
AUC_{0-60}, min × pg/mL	12,710	7538	169	117-242	90
AUC_{0-360}, min × pg/mL	34,130	21,250	161	117-220	73

Abbreviations: AUC_{0-x}, area under the curve from 0 to x minutes postdose; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; ENS, epinephrine nasal spray; GMR, geometric mean ratio; LSM, least squares mean; NAC, nasal allergen challenge; PK, pharmacokinetics.

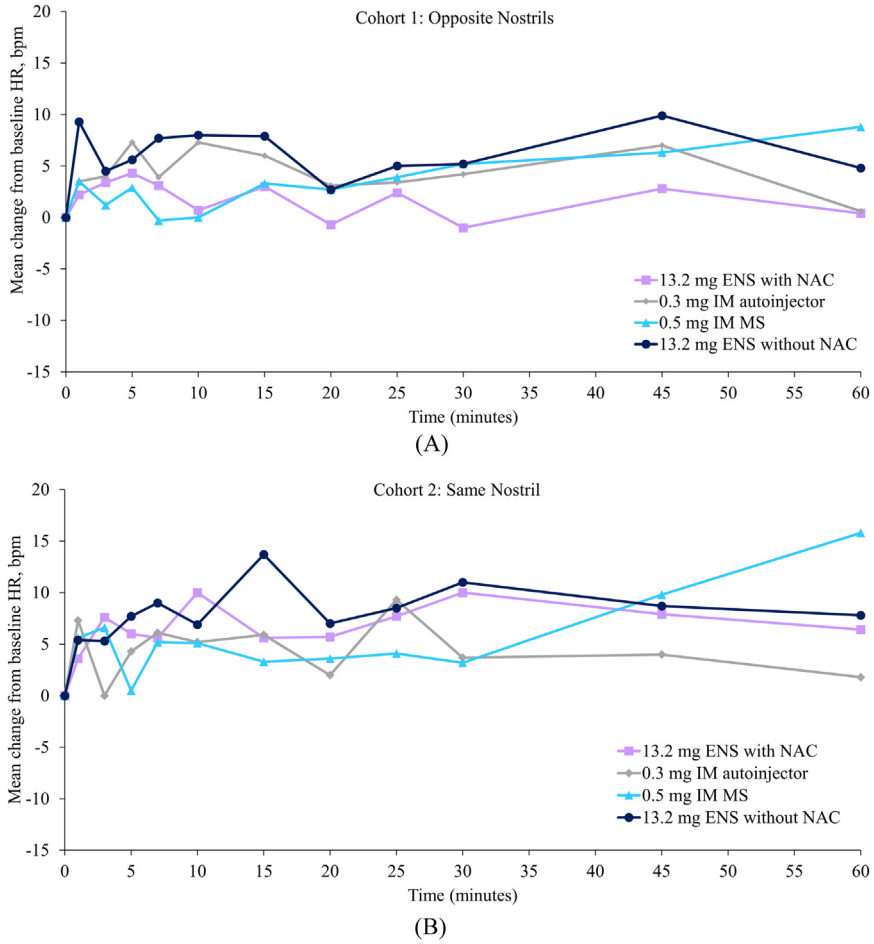

Figure 3. Mean change from baseline HR-time profiles after ENS administration with or without NAC or IM epinephrine administration in (A) cohort 1 (opposite nostrils) or (B) cohort 2 (same nostril). ENS, epinephrine nasal spray; HR, heart rate; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge.

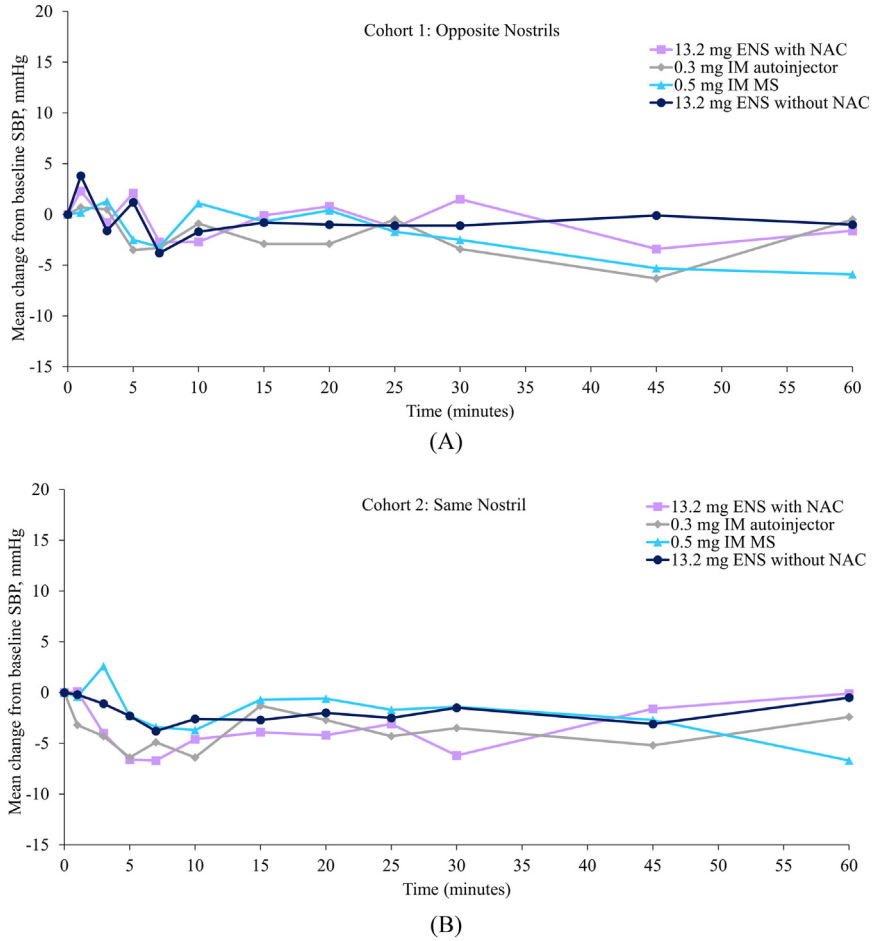

Figure 4. Mean change from baseline SBP-time profiles after ENS administration with or without NAC or IM epinephrine administration in (A) cohort 1 (opposite nostrils) or (B) cohort 2 (same nostril). ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge; SBP, systolic blood pressure.

Table 4
Treatment-Emergent Adverse Events Occurring in at Least 10% of Participants Receiving Epinephrine Nasal Spray With or Without Nasal Allergen Challenge or Intramuscular Epinephrine

	Cohort 1 (opposite nostrils) n = 26				Cohort 2 (same nostril) n = 25			
Subjects with TEAE, n (%)	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

Abbreviations: ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge; TEAE, treatment-emergent adverse event.

Safety

There were no serious AEs or discontinuations because of AEs during the study. The treatment-emergent AE incidences with the 13.2 mg ENS administration with and without NAC in cohort 1 were 54% and 64%, respectively, and in cohort 2 were 44% and 48%, respectively (Table 4). Nausea and headache were the most common AEs with the 13.2 mg ENS treatment (Table 4). Overall, on the basis of the data from both cohorts, 93% of treatment-emergent AEs were mild and 7% were moderate; 80% of treatment-emergent AE were assessed as likely or probably related to treatment. All AEs resolved with no sequelae.

All events of nausea and vomiting were assessed as mild. The median onset of nausea and vomiting was 41 and 106 minutes, respectively, and the median duration was 109 minutes and less than 1 minute, respectively.

Discussion

The results of this study in healthy adults revealed that the 13.2 mg dose of ENS administered as 2 sprays in either opposite nostrils or the same nostril had higher absorption in the presence of

allergen-induced nasal congestion than without congestion. Moreover, exposure to epinephrine after 13.2 mg ENS under congestion was also higher than with the reference IM epinephrine administrations by either autoinjector (0.3 mg) or MS (0.5 mg). Equivalent plasma concentrations were achieved as quickly with 13.2 mg ENS (with or without NAC) as with IM administration. The PD assessments revealed no clinically impactful effects of the 13.2 mg ENS on HR or BP regardless of the level of plasma epinephrine concentrations or epinephrine dosage form. Treatment with the 13.2 mg ENS appeared well tolerated.

Nasal congestion is a common symptom of anaphylaxis that is the result of vasodilation and increased vascular permeability.[11,12] Individuals with allergic rhinitis may also have nasal congestion in response to allergen exposure, and a NAC was previously reported to reliably induce the corresponding symptoms of nasal congestion in individuals with allergic rhinitis.[13] Extrapolation of the results of the NAC to the congestion associated with a food-related allergic reaction, one of the most common reasons for epinephrine use, is supported by a case report that evaluated nasal patency (measured by optimal rhinometry) and congestion (measured by visual analog scale) induced by a nasal food-allergen challenge and a double-blind, placebo-controlled oral food challenge in a patient with a severe allergy to chicken eggs.[14] Congestion induced by the nasal food-allergen challenge was greater than that induced by the oral challenge. Regardless of the cause of nasal congestion, if it impeded the absorption of intranasally administered epinephrine, then efficacy and/or safety could be affected. This study found that moderately severe allergen-induced congestion did not hinder the absorption of the 13.2 mg ENS; absorption was actually higher than under noncongestion conditions and compared with the IM treatments. This finding is in line with results from other studies evaluating the impact of nasal congestion on the absorption of intranasally-administered epinephrine.[15] Health care providers and patients can be assured that nasal congestion will not interfere with the ability of the ENS to deliver sufficient and well-tolerated concentrations of epinephrine into systemic circulation during an anaphylactic reaction.

The PD results of this study confirm previous observations that the 13.2 mg ENS has minimal, clinically insignificant effects on HR and BP.[16] There was no strong relationship between the PD effects and plasma epinephrine levels. Although this may be contrary to expected after the administration of epinephrine, the literature regarding the correlation between PD effects and epinephrine plasma levels is inconsistent, often with small sample sizes, inconsistent doses, and less-than-optimal blood sample collection times. Knowing that a correlation between PK and PD was not observed in the previous study,[16] the current study purposefully included continuous HR and BP monitoring accompanied by real-time monitoring to capture any PD changes to the degree capable of the electronic monitoring equipment. Every effort was made to decrease the number of variables to better be able to detect any changes in PD to then determine any relationship between the PD changes and PK. The PD effects were similar to those observed with reference to IM administration and were consistent with HR and BP findings in a previous study of IM epinephrine administration.[17]

The ability to self-administer epinephrine may be life-saving to individuals experiencing an anaphylactic reaction. However, studies clearly revealed that patients can be intimidated by IM autoinjectors and may fail to carry or use them as directed. One survey of 2000 adult and pediatric participants who filled prescriptions for an epinephrine IM autoinjector found that only half of the participants had carried their autoinjector all the time during the past 7 days.[18] In a study of 190 children aged 1 to 18 years who were prescribed epinephrine IM autoinjectors, 23% (n = 44) experienced an anaphylactic reaction requiring epinephrine during the 5-year study period, but only 3 children and 10 parents used the autoinjector.[5] The 13.2 mg ENS currently under development enables needle-free epinephrine administration. Health care professionals who participated in a multicenter, randomized study indicated a statistically significant preference for ENS over IM epinephrine autoinjectors in terms of portability, ease of use, safety, and likelihood of a patient using it in a real emergency.[19] Therefore, the use of ENS instead of IM autoinjectors has the potential to increase patient adherence and mitigate hospitalizations and death associated with failure to administer epinephrine in a timely manner.

The 13.2 mg ENS seemed well tolerated, with no serious or severe AEs. The AE profile differed between the 13.2 mg ENS and IM treatments, primarily reflected by the lack of injection site pain with ENS administration and the relatively lower incidence of gastrointestinal AEs with IM administration. Nausea and vomiting AEs with 13.2 mg ENS generally occurred within the period in which participants were having blood drawn for PK measures. These AEs were mild and transient, and all participants resumed their daily schedule without alteration on completion of the study.

A limitation of this study is that it was conducted outside of conditions of anaphylaxis because of ethical restrictions on inducing anaphylaxis. Such a study could be done in the future in which very well-controlled food or drug allergen challenges are administered in an allergen challenge clinic, and the 13.2 mg ENS could be used if rescue epinephrine is needed to reverse symptoms. The study is also limited by the small sample size.

In conclusion, this study found that with nasal congestion the absorption of the 13.2 mg ENS is enhanced. Nasal congestion does not seem to interfere with the absorption of epinephrine administered by means of nasal spray through the nasal mucosa and seems to allow for 13.2 mg ENS to adequately and safely deliver sufficient epinephrine concentrations compared with IM administration.

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Disclosures

Dr Dworaczyk was an employee of Bryn Pharma at the time of the study and currently provides consulting services for Bryn Pharma. Dr Rance is a current employee of Bryn Pharma. Dr Hunt, Mr Spirito, Ms Lor, and Dr van Haarst are employees of Celerion, which provides contract services for Bryn Pharma.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2024.04.033

References

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson Jr. NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391–397.
2. Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020;145(4):1082–1123.
3. Sicherer SH, Simons FER, Section on Allergy and Immunology. Epinephrine for first-aid management of anaphylaxis. *Pediatrics*. 2017;139(3): e20164006.

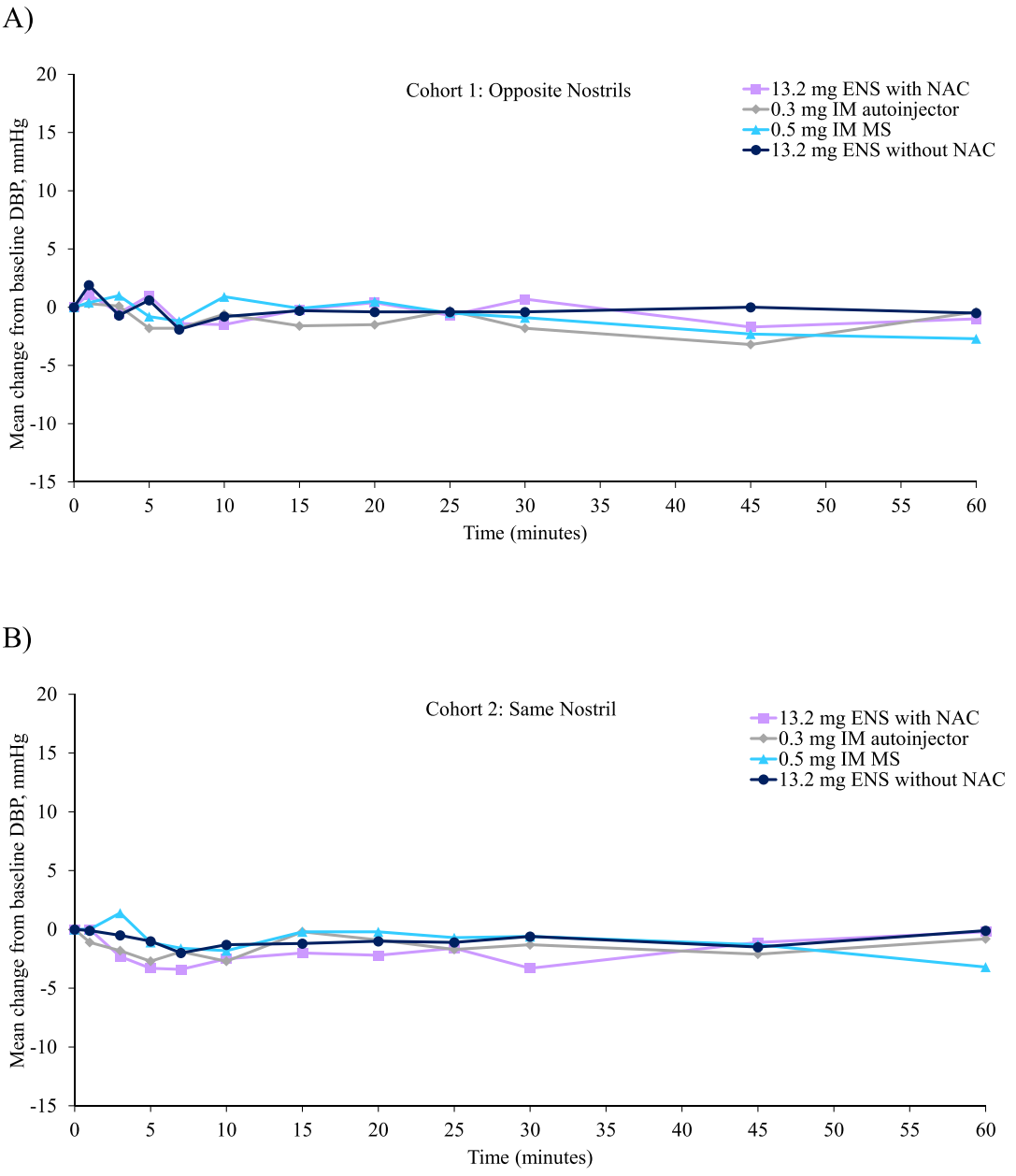
4. Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. *Clin Exp Allergy*. 2011;41(6):869–877.
5. Esenboga S, Ocak M, Cetinkaya PG, Sahiner UM, Soyer O, Buyuktiryaki B, et al. Physicians prescribe adrenaline autoinjectors, do parents use them when needed? *Allergol Immunopathol*. 2020;48(1):3–7.
6. Fleming JT, Clark S, Camargo Jr CA, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *J Allergy Clin Immunol Pract*. 2015;3(1):57–62.
7. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144–1150.
8. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol*. 2007;119(4):1016–1018.
9. *Data on File*. Bryn Pharma; 2023.
10. Allergic rhinitis: developing drug products for treatment. Guidance for industry Center for Drug Evaluation and Research. Food and Drug Administration. Accessed March 3, 2020. Available at: https://www.fda.gov/media/71158/download.
11. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis–a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341–384.
12. White MV. The role of histamine in allergic diseases. *J Allergy Clin Immunol*. 1990;86(4 Pt 2):599–605.
13. Ellis AK, Soliman M, Steacy L, Boulay ME, Boulet LP, Keith PK, et al. The Allergic Rhinitis–Clinical Investigator Collaborative (AR-CIC): nasal allergen challenge protocol optimization for studying AR pathophysiology and evaluating novel therapies. *Allergy Asthma Clin Immunol*. 2015;11(1):16.
14. Krzych-Fałta E, Wojas O, Samel-Kowalik P, Samoliński B, Sybilski A, Białek S. Oral and nasal provocation test in chicken egg allergy-case report. *Allergy Asthma Clin Immunol*. 2023;19(1):70.
15. Tal Y, Ribak Y, Rubin L, Talmon A, Shamriz O, Hershko AY, et al. Fast acting, dry powder, needle-free, intranasal epinephrine spray: a promising future treatment for anaphylaxis. *J Allergy Clin Immunol Pract*. 2023;11(10):3047–3054.
16. Dworaczyk DA, Hunt AL, DiSpirito M, Lor M, Dretchen K, Lamson M, et al. 13.2 mg intranasal epinephrine spray demonstrates comparable pharmacokinetics, pharmacodynamics, and safety to 0.3 mg epinephrine autoinjector. *J Allergy Clin Immunol Glob*. 2023;3: 100200.
17. Worm M, Nguyen D, Rackley R, Muraro A, Du Toit G, Lawrence T, et al. Epinephrine delivery via EpiPen(®) Auto-Injector or manual syringe across participants with a wide range of skin-to-muscle distances. *Clin Transl Allergy*. 2020;10:21.
18. Portnoy J, Wade RL, Kessler C. Patient carrying time, confidence, and training with epinephrine autoinjectors: the RACE survey. *J Allergy Clin Immunol Pract*. 2019;7(7):2252–2261.
19. Soosaar J, Japp S, Johnstone S, Pohl E, Fairchild S, Anderson P, et al. Multicenter, randomized crossover healthcare profession preference study of bidose epinephrine nasal spray vs epinephrine autoinjector. *Ann Allergy Asthma Immunol*. 2019;123(5):S20.

Supplementary Data

eTable 1
Change From Baseline Heart Rate, Systolic Blood Pressure, and Diastolic Blood Pressure Maximum Positive Effect Level After Epinephrine Nasal Spray With or Without Nasal Allergen Challenge or Intramuscular Epinephrine in Cohort 1 (Opposite Nostrils) and Cohort 2 (Same Nostril)

Parameter, cohort	Comparison	LS means, test	LS means, reference	LS mean difference	LS mean difference 90% CI
HR bpm, cohort 1	13.2 mg ENS with NAC vs IM autoinjector	21.9	28.0	−6.1	−13.4 to 1.2
	13.2 mg ENS with NAC vs IM MS	21.9	25.6	−3.7	−11.0 to 3.6
	13.2 mg ENS without NAC vs IM autoinjector	26.7	28.0	−1.3	−8.7 to 6.1
	13.2 mg ENS without NAC vs IM MS	26.7	25.6	1.1	−6.3 to 8.5
HR bpm, cohort 2	13.2 mg ENS with NAC vs IM autoinjector	32.1	33.3	−1.2	−8.4 to 5.9
	13.2 mg ENS with NAC vs IM MS	32.1	32.9	−0.8	−8.0 to 6.4
	13.2 mg ENS without NAC vs IM autoinjector	37.9	33.3	4.6	−2.6 to 11.7
	13.2 mg ENS without NAC vs IM MS	37.9	32.9	5.0	−2.2 to 12.2
SBP mmHg, cohort 1	13.2 mg ENS with NAC vs IM autoinjector	19.0	12.9	6.1	1.1 to 11.1
	13.2 mg ENS with NAC vs IM MS	19.0	15.9	3.2	−1.8 to 8.1
	13.2 mg ENS without NAC vs IM autoinjector	17.2	12.9	4.3	−0.72 to 9.3
	13.2 mg ENS without NAC vs IM MS	17.2	15.9	1.4	−3.6 to 6.4
SBP mmHg, cohort 2	13.2 mg ENS with NAC vs IM autoinjector	21.9	13.8	8.2	1.7 to 14.6
	13.2 mg ENS with NAC vs IM MS	21.9	16.1	5.8	−0.6 to 12.3
	13.2 mg ENS without NAC vs IM autoinjector	19.5	13.8	5.7	−0.8 to 12.2
	13.2 mg ENS without NAC vs IM MS	19.5	16.1	3.4	−3.1 to 9.9
DBP mmHg, cohort 1	13.2 mg ENS with NAC vs IM autoinjector	13.9	9.4	4.5	1.3 to 7.7
	13.2 mg ENS with NAC vs IM MS	13.9	10.5	3.4	0.3 to 6.6
	13.2 mg ENS without NAC vs IM autoinjector	12.8	9.4	3.4	0.2 to 6.6
	13.2 mg ENS without NAC vs IM MS	12.8	10.5	2.3	−0.9 to 5.5
DBP mmHg, cohort 2	13.2 mg ENS with NAC vs IM autoinjector	15.1	9.4	5.7	1.8 to 9.5
	13.2 mg ENS with NAC vs IM MS	15.1	10.6	4.5	0.7 to 8.4
	13.2 mg ENS without NAC vs IM autoinjector	13.9	9.4	4.5	0.6 to 8.3
	13.2 mg ENS without NAC vs IM MS	13.9	10.6	3.3	−0.5 to 7.2

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; ENS, epinephrine nasal spray; HR, heart rate; IM, intramuscular; LS, least squares; MS, manual syringe; NAC, nasal allergen challenge; SBP, systolic blood pressure.



eFigure 1. Mean change from baseline DBP-time profiles after ENS with or without NAC or IM epinephrine in (A) cohort 1 (opposite nostrils) or (B) cohort 2 (same nostril). DBP, diastolic blood pressure; ENS, epinephrine nasal spray; IM, intramuscular; MS, manual syringe; NAC, nasal allergen challenge.