

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

David Dworaczky, PhD,¹ Allen Hunt, MD², Mike Di Spirito, MSc³, Mary Lor, BSc, GrDip³
¹Bryn Pharma, LLC, Raleigh, NC, USA; ²Celerion, Lincoln, NE, USA; ³Celerion, Montreal, QC, Canada

INTRODUCTION

- Epinephrine is the first-line treatment for anaphylaxis and is typically administered by an intramuscular (IM) autoinjector¹
- 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 outcomes²⁻⁴
- 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 congestion⁵

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

	Cohort 1 (Opposite Nostrils) N=26	Cohort 2 (Same Nostril) N=25
Characteristic		
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

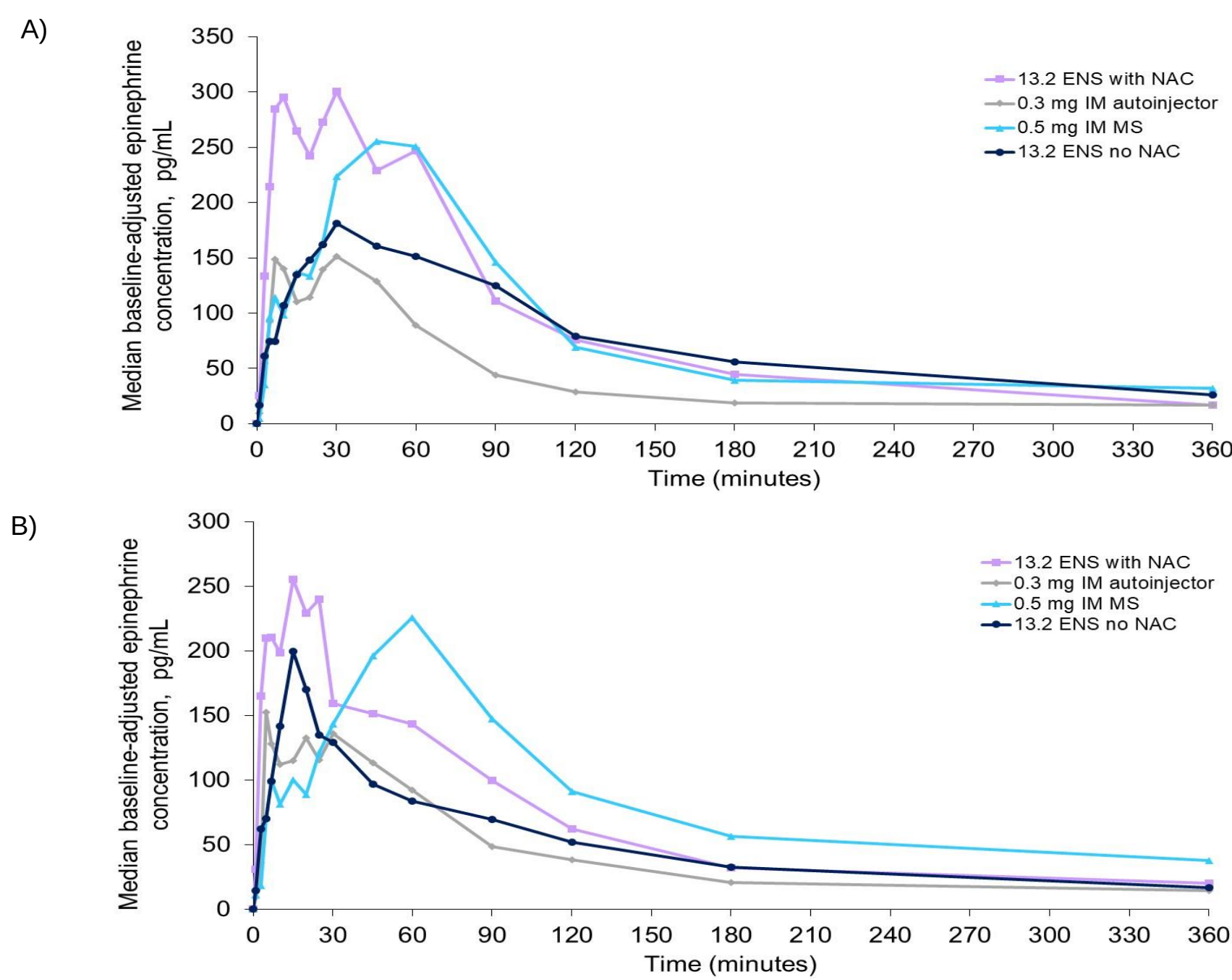
PD

- 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)

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

PK Parameter	Cohort 1 (Opposite Nostrils)		GMR, %	90% CIs	Intrasubject CV%
	13.2 ENS with NAC Geometric LSM	13.2 ENS without NAC Geometric LSM			
C _{max} , pg/mL	458	270	170	123-234	78
AUC _{0–360} , min*pg/mL	34,200	29,500	116	91-149	57

PK Parameter	Cohort 2 (Same Nostril)		GMR, %	90% CIs	Intrasubject CV%
	13.2 ENS with NAC Geometric LSM	13.2 ENS without NAC Geometric LSM			
C _{max} , pg/mL	435	250	174	115-263	107
AUC _{0–360} , min*pg/mL	34,130	21,250	161	117-220	73

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

	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
Subjects with TEAE, n (%)	14 (54)	4 (15)	7 (27)	16 (64)	11 (44)	4 (16)	5 (20)	12 (48)
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

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).

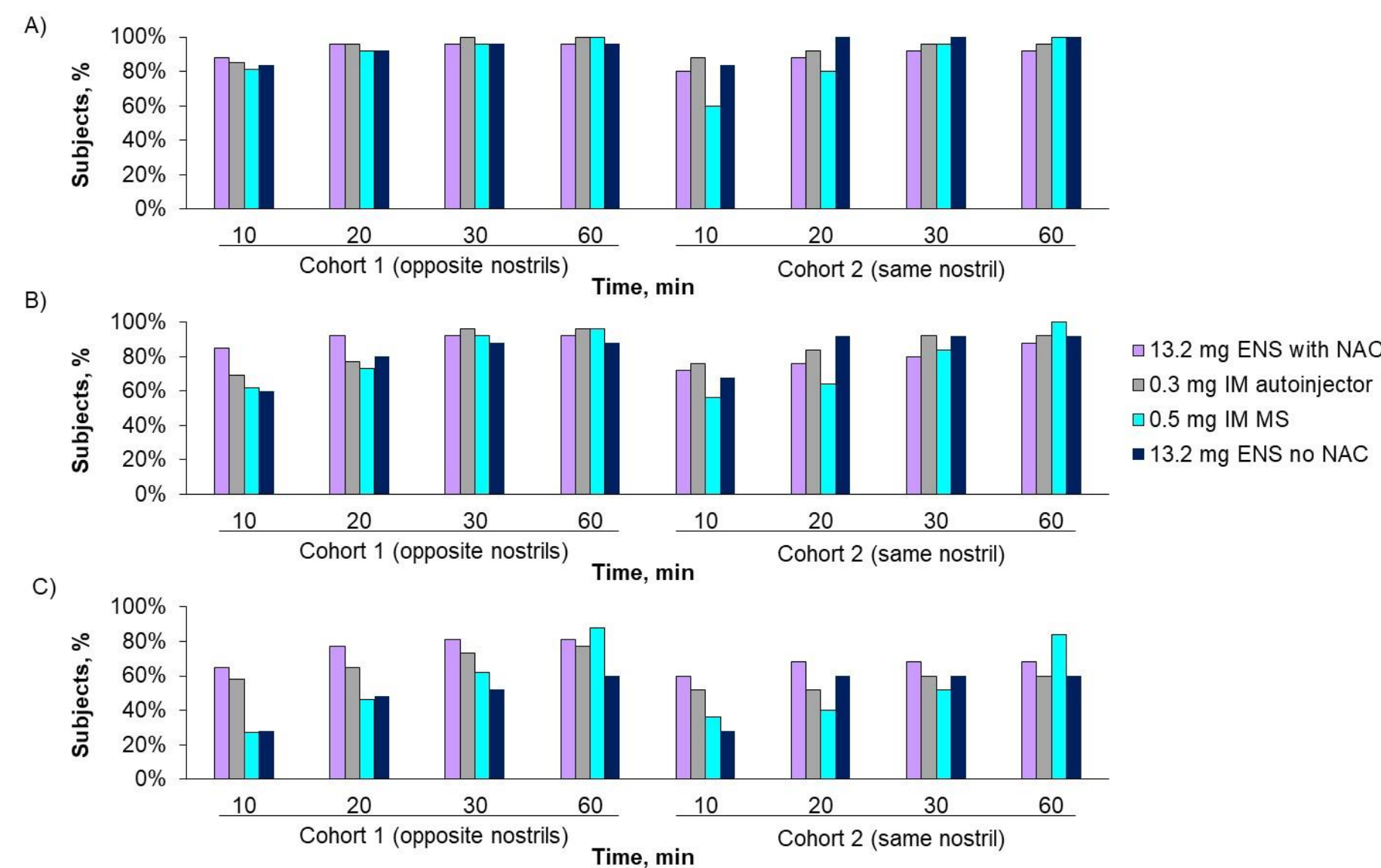
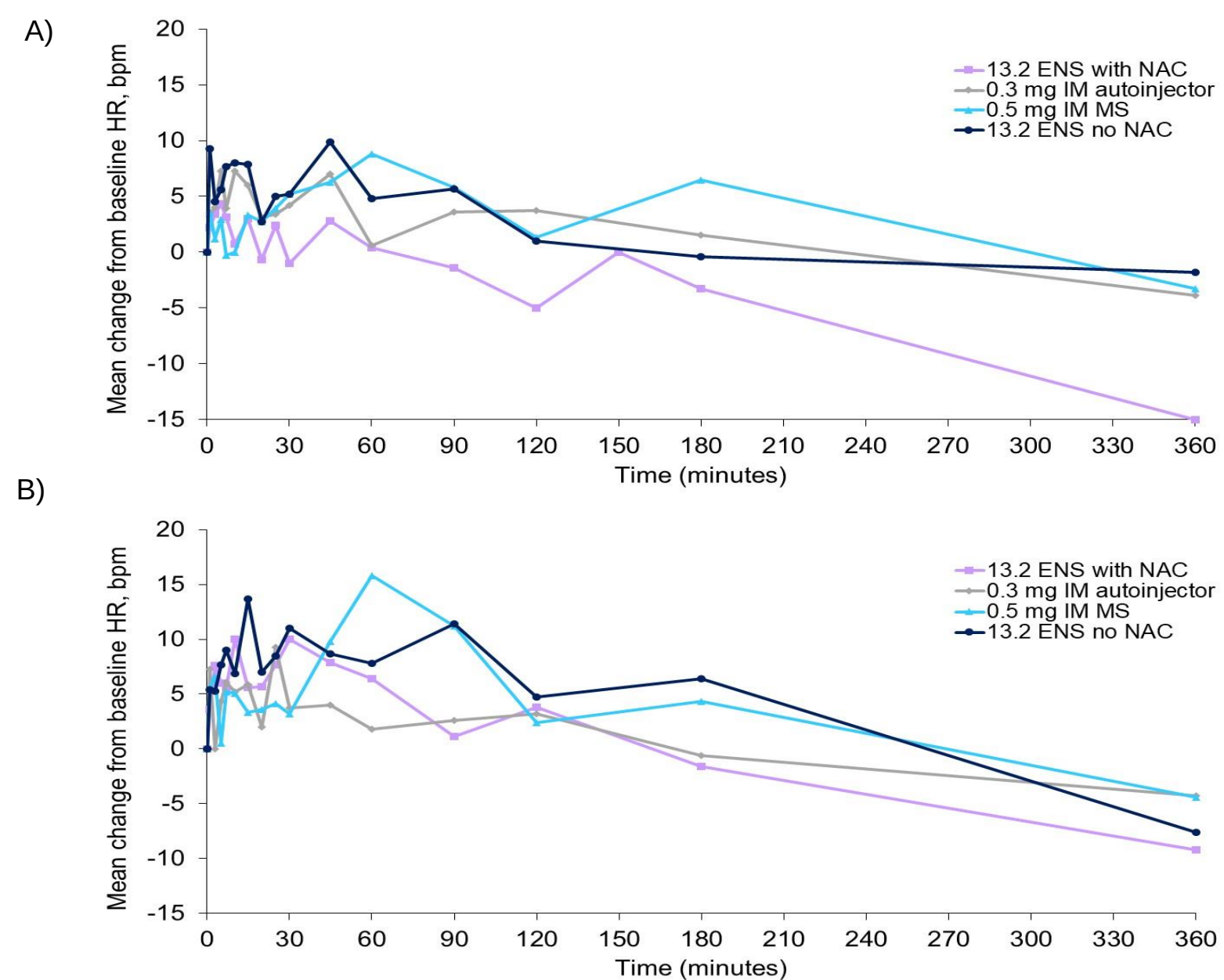


Figure 3. Mean change from baseline heart rate – time profiles after ENS with or without NAC or IM epinephrine in A) Cohort 1 (opposite nostrils) or B) Cohort 2 (same nostril).



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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