Poster #L48

Pharmacokinetics and Safety of Repeat Dosing with Epinephrine Nasal Spray in Healthy Adults

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INTRODUCTION

- Epinephrine is the first-line treatment for anaphylaxis, which is a serious allergic reaction to food, medications, insect venom, and other environmental allergens[1]
- Epinephrine needs to be administered quickly after the onset of anaphylaxis to mitigate morbidity and potentially even death[2]
- Approximately 8% of patients experiencing anaphylaxis are treated with more than 1 dose of epinephrine[3]
  - The repeat dose may be required within 5-15 minutes after the first administration[4]
- An epinephrine nasal spray (ENS; NDS1C, Bryn Pharma, Lebanon, NJ) is under development for the treatment of anaphylaxis

OBJECTIVE

- To assess the pharmacokinetics (PK) and safety of repeat doses of 13.2 mg ENS in healthy adults

METHODS

Study design

- This was an open-label crossover phase I study conducted in healthy adults
- In a crossover fashion of 3 treatment periods, participants were randomized to a treatment period sequence in which they received:
  - 2 doses of 13.2 mg ENS 5 minutes apart administered to opposite nostrils (ON)
    - A single dose consisted of 2 consecutive sprays of 6.6 mg each administered within 10 seconds of each other to ON
  - 2 doses of 13.2 mg ENS 5 minutes apart administered to the same nostril (SN)
    - A single dose consisted of 2 consecutive sprays of 6.6 mg each administered within 10 seconds of each other to the SN
  - A single dose of 13.2 mg ENS
    - A single dose consisted of 2 consecutive sprays of 6.6 mg each administered within 10 seconds of each other to ON
- There was a washout period of approximately 14 days between 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 $AUC_{0–360}$)

Safety analysis

- Heart rate and blood pressure 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
- Continuous telemetry for monitoring of cardiac rhythm was performed from 60 minutes predose to 180 minutes postdose
- Participants were monitored for adverse events (AEs) throughout the study

Statistical analysis

- Summary statistics 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

Conclusion

- A repeat dose of 13.2 mg ENS within 5 minutes increases epinephrine absorption by approximately 50% with no notable effect on PD or safety compared with a single dose

Statistical analysis cont.

- For HR, an ANOVA was performed by treatment 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
- Baseline values used for adjustment of plasma epinephrine concentrations, heart rate, and blood pressure were an average of 3 predose measurements

RESULTS

Participants

- Overall, 36 participants were enrolled in the study and 35 completed the study; 1 participant discontinued for personal reasons
- In the study population, 47% were female, 67% were White, and the mean age was 40.4 years

PK

- Absorption of epinephrine increased by approximately 50% after repeat dosing with 13.2 mg ENS ON or SN compared with a single dose (**Figure 1**)
- The repeated dose 13.2 mg ENS in ON or SN had higher overall and peak exposures than single dose 13.2 mg ENS (**Table 1**)
- Median T_{max} was comparable between the 3 groups at 26 minutes for repeat dosing in ON, 29 minutes for repeat dosing in SN, and 25 minutes for the single dose (**Table 1**)
- The geometric mean ratios of C_{max} and AUC_{0-360} with repeat dosing ranged from 160-177% compared with a single dose (**Table 2**)

Safety

- There was a trend toward higher heart rate with repeat dosing compared with a single dose (**Figure 2**), but the LSM difference in change from baseline in E_{max} heart rate values were not significantly different (6.6 bpm [90% CI: −1.6, 14.8] between repeat dosing in ON and single dosing and 6.9 bpm [90% CI: −1.3, 15.0] between repeat dosing in SN and single dosing)
  - Effects on blood pressure were similar between repeat dosing and a single dose (**Figure 3**)
- There were no AEs of tachycardia associated with palpitations with any of the treatments
- The overall AE profile with repeat dosing was similar to a single dose (**Table 3**)
  - There was a trend toward a higher percentage of participants reporting upper abdominal pain, nasal discomfort, and nausea with repeat dosing compared with the single dose
  - 93% of AEs were mild in severity

Table 1. Baseline-adjusted plasma epinephrine PK parameters

PK Parameter	13.2 mg ENS Repeated Dose ON N=36	13.2 mg ENS Repeated Dose SN N=36	13.2 mg ENS Single Dose N=35
C_{max}, pg/mL, geometric mean (CV%)	394 (107)	417 (156)	238 (86)
C_{max20}, pg/mL, geometric mean (CV%)	269 (143)	281 (180)	150 (195)
T_{max}, min, median (minimum, maximum)	26 (7, 181)	29 (7, 90)	25 (3, 362)
AUC_{0-10}, pg*min/mL, geometric mean (CV%)	603 (186)	654 (199)	531 (152)
AUC_{0-20}, pg*min/mL, geometric mean (CV%)	2,589 (151)	2,787 (192)	1,468 (329)
AUC_{0-30}, pg*min/mL, geometric mean (CV%)	5,245 (133)	5,627 (172)	3,265 (115)
AUC_{0-60}, pg*min/mL, geometric mean (CV%)	12,660 (110)	13,440 (146)	8,038 (86)
AUC_{0-360}, pg*min/mL, geometric mean (CV%)	42,840 (95)	40,610 (119)	25,700 (71)

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; ON, opposite nostrils; SN, same nostril; T_{max}, time to reach maximum concentration.

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

PK Parameter	13.2 mg ENS Repeated Dose ON Geometric LSM	13.2 mg ENS Single Dose Geometric LSM	GMR, %	90% CIs	Intrasubject CV%
C_{max}, pg/mL	385	236	163	124-215	79
AUC_{0-360}, pg*min/mL	42,118	25,456	165	128-213	70
	13.2 mg ENS Repeated Dose SN	13.2 mg ENS Single Dose			
C_{max}, pg/mL	417	236	177	135-233	79
AUC_{0-360}, pg*min/mL	40,607	25,456	160	124-205	70

AUC_{0-360}, area under the curve from 0 to 360 minutes postdose; C_{max}, maximum observed concentration; CV, coefficient of variation; ENS, epinephrine nasal spray; GMR, geometric mean ratio; LSM, least-squares means; ON, opposite nostrils; SN, same nostril.

REFERENCES

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Table 3. Summary of participants reporting AEs

AE parameter, n (%)	13.2 mg ENS Repeated Dose ON N=36	13.2 mg ENS Repeated Dose SN N=36	13.2 mg ENS Single Dose N=35
TEAE	21 (58)	26 (72)	18 (51)
SAE	0	0	0
Discontinuations due to AEs	0	0	0
Severe TEAE	0	0	0
Most common TEAEs*			
Upper abdominal pain	11 (31)	9 (25)	6 (17)
Nasal discomfort	10 (28)	11 (31)	4 (11)
Nausea	7 (19)	9 (25)	4 (11)
Headache	7 (19)	8 (22)	7 (20)
Vomiting	4 (11)	8 (22)	4 (11)
Abdominal discomfort	1 (3)	6 (17)	0
Rhinorrhea	0	2 (6)	6 (17)

ENS, epinephrine nasal spray; ON, opposite nostrils; SAE, serious adverse event; SN, same nostril; TEAE, treatment-emergent adverse event.
*≥10% in any treatment group.

Figure 1. Geometric mean baseline-adjusted plasma epinephrine concentration – time profiles (log scale)

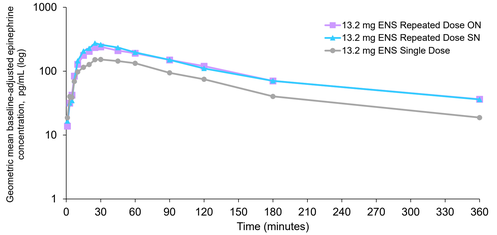

Figure 2. Mean change from baseline heart rate (HR) – time profiles

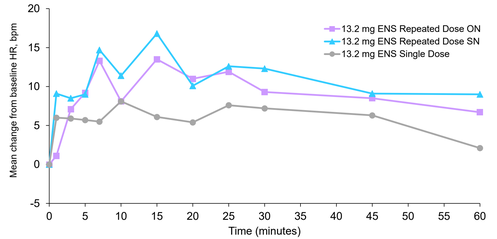

Figure 3. Mean change from baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) – time profiles