Poster # L01

13.2mg Intranasal Epinephrine Spray Demonstrates Comparable PK/PD and Safety to 0.3mg Epinephrine Autoinjector

David Dworaczyk, PhD,[1] and Allen Hunt, MD[2]

[1]Bryn Pharma, LLC, Raleigh, NC, USA; [2]Celerion, Lincoln, NE, USA

2023 AAAAI ANNUAL MEETING

INTRODUCTION

- Type I hypersensitivity is an immediate reaction that involves immunoglobulin E-mediated release of antibodies against a soluble antigen, which results in mast cell degranulation and release of histamine and other inflammatory mediators.[1]
- Type I allergic reactions vary in severity on the allergen and the individual's specific immunological reaction to exposure.[2]
- Some allergens, such as foods, drugs, and insect venoms, can lead to serious hypersensitivity reactions, which may result in anaphylaxis.[1]
- Anaphylaxis is a serious acute allergic reaction that requires immediate attention to avoid serious morbidity and mortality.
- Epinephrine is the first-line therapy for anaphylaxis, commonly administered via intramuscular (IM) autoinjector[3] in an outpatient setting.
- Patient use of autoinjectors is decreased due to not carrying their devices routinely, reluctance to use a self-injector (e.g., needle anxiety or fear), or application error (e.g., lack of training, injection injuries).[3-7]
- Delayed epinephrine administration or suboptimal exposure during anaphylactic events may increase the risk of hospitalizations and potentially fatal outcomes.[8]
- Intranasal (IN) administration has been explored for the treatment of acute anaphylactic reactions.[9-12]
- Nasal sprays have been successfully developed for several acute interventions requiring rapid onset of action and administration outside of the healthcare setting, such as NARCAN for the treatment of opioid overdose and intranasal glucagon for the treatment of acute hypoglycemia in patients with diabetes.[13,14] Similarly, intranasal administration of epinephrine is an attractive option for the acute treatment of patients experiencing an anaphylactic event.

RATIONALE

- NDS1C 13.2 mg is a self-administered, intranasal dosage form of epinephrine (bi-dose 6.6 mg epinephrine spray) intended for the treatment of type 1 allergic reactions, including anaphylaxis.
- In previous studies with smaller sample sizes, the systemic exposure over 6 hours ($AUC_{0\text{-}360}$) and C_{max} achieved following IN administration of 2 consecutive doses of 6.6 mg epinephrine to opposite nostrils was higher than that of the reference 0.3 mg IM autoinjector dose.
- This pivotal study was conducted to confirm the results observed in the dose-ranging study by comparing the relative bioavailability (BA) of a single 13.2mg IN dose of epinephrine (administered as 2×6.6 mg sprays administered into each or the same nostril) to that of IM-administered epinephrine via autoinjector (0.3 mg) the primary reference, and prefilled manual syringe (0.5 mg).
- In addition, this study was structured to assess the number of subjects meeting key plasma concentrations at prespecified time points, and to assess the relative PD, safety, and tolerability of IN epinephrine compared to epinephrine administered via IM injection.

PRIMARY AND SECONDARY OBJECTIVES

Primary Objective

- To compare the PK of a single IN dose of epinephrine (consisting of 2 consecutive sprays administered to either the same or opposite nostrils) to that of a single IM injection via autoinjector and manual syringe in healthy adult subjects.

Secondary Objectives

- To assess the proportion of subjects reaching unadjusted and baseline-adjusted epinephrine concentrations of 50, 100, and 200 pg/mL at 10-, 20-, 30-, and 60-minutes post-dose following IN administrations of epinephrine in healthy adult subjects.
- To assess the time after IN administration to reach unadjusted and baseline-adjusted epinephrine concentrations equal to epinephrine C_{max} following IM administration via autoinjector in healthy adult subjects.
- To compare the PD effect (expressed as changes in BP and HR) of IN administrations of epinephrine to that of epinephrine administered via IM autoinjector in healthy adult subjects.
- To assess the safety and tolerability of epinephrine following a single IN dose of epinephrine (consisting of 2 consecutive sprays) in healthy adult subjects.

METHODS

Study Design

- The study was conducted using an open-label, 3-period, 2-cohort, crossover design to assess the relative bioavailability (BA) of a single intranasal dose of epinephrine 13.2mg consisting of 2 consecutive 6.6 mg sprays, compared to an intramuscular 0.3 mg autoinjector, the primary reference product and 0.5 mg manual syringe.
- Each cohort was conducted in a 3-period, 3-treatment, crossover fashion, with all subjects within a given cohort receiving the same IN treatment in Period 1, followed by 1 of 2 IM treatments in Period 2, and then the other of the 2 IM treatments in Period 3, per the randomization scheme.
- Dosing of Cohort 2 did not begin until all subjects in Cohort 1 completed Period 1 dosing, and a washout period of 24 hours was included between doses.

STUDY COHORT

COHORT 1		COHORT 2	
Treatment A: (Period 1)	13.2 mg epinephrine administered as two IN sprays of 6.6 mg (0.11 mL x 60 mg/mL NDS1C) by nasal spray immediately* one after the other to opposite nostrils at Hour 0 on Day 1, using the same device	Treatment D: (Period 1)	13.2 mg epinephrine administered as two IN sprays of 6.6 mg (0.11 mL x 60 mg/mL NDS1C) by nasal spray immediately* one after the other to the same nostrils at Hour 0 on Day 1, using the same device
Treatment B: (Period 2 or 3)	0.3 mg epinephrine (0.3 mL x 1 mg/mL Epinephrine Injection, USP Auto-Injector 0.3 mg [Mylan, authorized generic for EpiPen®]) administered via IM injection at Hour 0 on Day 1	Treatment E: (Period 2 or 3)	0.3 mg epinephrine (0.3 mL x 1 mg/mL Epinephrine Injection, USP Auto-Injector 0.3 mg [Mylan, authorized generic for EpiPen®]) administered via IM injection at Hour 0 on Day 1
Treatment C: (Period 2 or 3)	0.5 mg epinephrine (0.5 mL x 1 mg/mL Epinephrine Injection, USP solution) administered via IM injection (manual syringe) at Hour 0 on Day 1	Treatment F: (Period 2 or 3)	0.5 mg epinephrine (0.5 mL x 1 mg/mL Epinephrine Injection, USP solution) administered via IM injection (manual syringe) at Hour 0 on Day 1

** The 2 consecutive IN sprays were administered within no more than 10 seconds of each other*

Conclusions

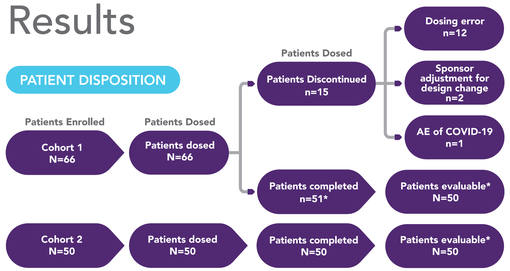
- The 13.2 mg epinephrine IN treatment administered to opposite and same nostrils showed rapid absorption and resulted in higher and more sustained therapeutic epinephrine plasma levels compared to the 0.3 mg epinephrine IM autoinjector.
- When the IN treatment was compared with the 0.5 mg epinephrine IM manual syringe, PK parameters were higher, with the only exception being $AUC_{0\text{-}Tmax}$ which was 37% lower.
- These results demonstrate that IN epinephrine provides an enhanced PK profile (higher and more sustained) compared to the standard reference product, the 0.3 mg epinephrine autoinjector.
- Mean unadjusted and baseline-adjusted vital sign values for HR, SBP, and DBP were generally within normal limits across all treatments for both cohorts with post-dose values remaining stable and relatively similar to pre-dose values.
- These data support the ability of 13.2mg IN epinephrine to achieve therapeutic levels of epinephrine rapidly and to maintain those levels essentially twice as long as those achieved using the 0.3 mg IM autoinjector with a similar safety profile to IM epinephrine.

STATISTICAL ANALYSIS

- All epinephrine PK concentrations and PK parameters descriptive statistics were generated using SAS® Version 9.4. Summary statistics, including sample size (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum were calculated for all nominal concentration time points. Summary statistics (n, mean, SD, CV%, SEM, minimum, median, maximum, geometric mean, and geometric CV%) were calculated for plasma epinephrine PK parameters.
- All HR and BP unadjusted and baseline-adjusted measurements and PD parameters descriptive statistics were generated using SAS® Version 9.4. Summary statistics, including n, mean, SD, CV%, SEM, minimum, median, and maximum were calculated for all nominal collection time points.
- Comparisons of interest included, for Cohort 1, Treatment A compared with Treatment B and Treatment A compared with Treatment C, and for Cohort 2, Treatment D compared with Treatment E and Treatment D compared with Treatment F.

Results

PATIENT DISPOSITION



**One patient who completed the study in Cohort 1 was not included in the evaluable population due to being dosed before the amendment and had received 3 doses, but the last one was the same as the first IN dose.*

PHARMACOKINETICS

- The 13.2 mg IN dose administered in the opposite or same nostrils resulted in overall higher and more sustained epinephrine plasma concentrations compared to the 2 IM treatments studied, with a rate of absorption comparable to the 0.3 mg IM autoinjector with a higher therapeutic level of epinephrine (i.e. >100 pg/mL) for essentially twice as long as the 0.3 mg autoinjector.
- The baseline adjusted PK parameters for 13.2 mg IN opposite nostril dosing were higher compared to the 0.3 mg epinephrine autoinjector, with the exception of $AUC_{0\text{-}10}$ which was essentially the same.
- The baseline adjusted PK parameters for 13.2 mg IN same nostril dosing had lower epinephrine plasma concentrations compared to opposite nostril IN dosing and were higher than the 0.3 mg autoinjector
- Peak epinephrine concentrations occurred earlier for the 0.3 mg epinephrine IM auto injector and IN treatments (median T_{max} within 20 minutes) and later for the 0.5 mg epinephrine IM manual syringe (median T_{max} of 45 minutes).
- Overall, the proportions of subjects who attained epinephrine plasma concentration thresholds of 50, 100, or 200 pg/mL at 10-, 20-, 30-, and 60-minutes post-dose were as good as or better than the 0.3 mg autoinjector for both opposite and same nostril IN dosing.

PHARMACODYNAMIC RESULTS

Heart rate

- Median Emax values for baseline-adjusted HR were > 20 bpm across all treatments in both cohorts. The differences in baseline-adjusted HR values between nasal administration (same and opposite nostrils) and IM administration (autoinjector and manual syringe) were not statistically significant.

Blood pressure

- In both cohorts 1 and 2, no baseline changes for SBP were observed that were > 20 mmHg or for DBP > ±10 mmHg.

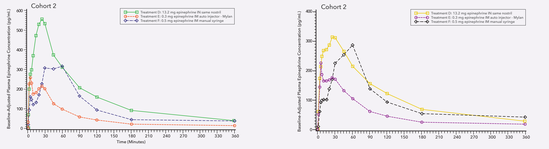
PD summary

- Overall, there were no statistical or clinically meaningful differences in HR or BP across all treatment groups (IN and IM administered).
- Additionally, the pattern of changes and the magnitude of the effects were similar across all PD parameters evaluated.

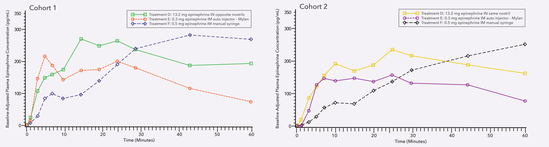
SAFETY RESULTS

- There were no deaths, SAEs, or laboratory related events reported in this study.
- One subject was discontinued due to the treatment unrelated AE of COVID-19 in Cohort 1.
- Of the 219 events in Cohort 1 (reported by 74% of subjects overall), the PI considered the majority (181) to be mild in severity. Of the 105 events in Cohort 2 (reported by 66% of subjects overall), the PI considered the majority (103) to be mild in severity, were transient and resolved relatively quickly with no sequelae.
- The most common event reported in Cohort 1 was headache (20 [30%] subjects, overall) and in Cohort 2 mild vomiting was the most common, reported by 8 (16%) subjects overall (following nasal administration alone), generally occurring 1-4hrs post dose and which may be related to swallowing the non-absorbed epinephrine.
- Nasal related AEs were minimally reported in each cohort as were injection site events.
- Overall, the safety results for IN epinephrine and IM administration routes were comparable, demonstrating that the IN dosage was well tolerated and that there were no new safety signals for the IN route of administration.

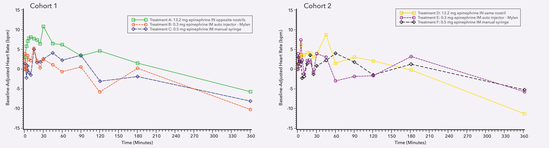
MEAN BASELINE ADJUSTED PLASMA EPINEPHRINE CONCENTRATION-TIME PROFILES (0-360 MIN POST-DOSE)



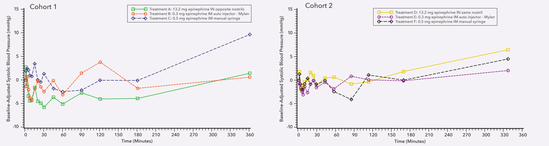
MEDIAN BASELINE ADJUSTED PLASMA EPINEPHRINE CONCENTRATION-TIME PROFILES (0-60 MIN POST-DOSE)



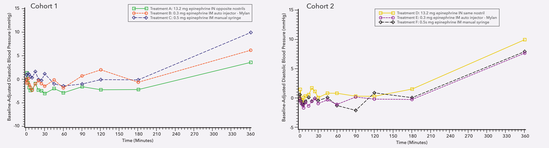
BASELINE-ADJUSTED HEART RATE-TIME PROFILES



BASELINE-ADJUSTED SBP-TIME PROFILES OBSERVED IN COHORTS 1 AND 2



BASELINE-ADJUSTED DBP-TIME PROFILES OBSERVED IN COHORTS 1 AND 2



REFERENCES

1. Simons FER. Anaphylaxis: Recent advances in assessment and treatment. *J Allergy Clin Immunol.* 2009;124(4):625-636. doi:10.1016/j.jaci.2009.08.025.
2. Justiz Vaillant AA, Vashisht R, Zito PM. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Apr 4, 2022. Immediate Hypersensitivity Reactions.
3. Posner LS, Camargo CA Jr. *Drug Healthc Patient Saf.* 2017;9:9–18.
4. Niño de Guzmán Quispe E, Martínez García L, Orrego Villagrán C, et al. *Patient.* 2021;14(6):719-740.
5. Uhm JY, Choi MY. *Healthcare (Basel).* 2020;8(4):506.
6. Bellanti JA, Settipane RA. *Allergy Asthma Proc.* 2014;35(3):195–196.
7. Simons FER, Ebisawa M, Sanchez-Borgas M, et al. *World Allergy Organ J.* 2015;8(1):32.
8. McLenon J and Rogers MAM. *J Adv Nurs.* 2019;75(1):30–42.
9. Portnoy J, Wade RL, Kessler C. *J Allergy Clin Immunol Pract.* 2019;7(7):2252–2261.
10. Fleming JT, Clark S, Camargo CA Jr., Rudders SA. *J Allergy Clin Immunol Pract.* 2015;3(1):57–62.
11. Srisawat C, Nakponetong K, Benjasupattananun P, et al. *Asian Pac J Allergy Immunol.* 2016;34(1):38–43.
12. McDonald R, Lorch U, Woodward J, et al. *Addiction.* 2018;113(3):484–493.
13. NARCAN (naloxone hydrochloride) Nasal Spray Prescribing Information, issued 11/2020.
14. Lowe RN, Trujillo JM. *Ann Pharmacother.* 2020;54(8):780-787.

ACKNOWLEDGMENTS AND DISCLOSURES

- This research was supported by Bryn Pharma, LLC. Medical writing assistance was provided by Alden Masonis, PhD, and Donna Schroeder, PharmD of ODIN's Strategic Solutions; funding for this assistance was provided by Bryn Pharma, LLC.
- David Dworaczyk, PhD, is an employee of Bryn Pharma, LLC. Allen Hunt, MD, is an employee of Celerion and received funding support from Bryn Pharma, LLC, to conduct this research study.