Original Article

Fast Acting, Dry Powder, Needle-Free, Intranasal Epinephrine Spray: A Promising Future Treatment for Anaphylaxis

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What is already known about this topic? Epinephrine autoinjectors are significantly underused for the emergency treatment of allergic reactions (type I), including anaphylaxis.

What does this article add to our knowledge? FMXIN002, a dry powder intranasal epinephrine spray, is safe, fast absorbed, stable at room temperature, and needle free. However, it has not yet been tested on specific populations, and variability between individuals may exist regarding its systemic uptake.

How does this study impact current management guidelines? Epinephrine nasal powder spray may be a suitable alternative to EpiPen intramuscular with certain advantages.

BACKGROUND: Epinephrine intramuscular (IM) autoinjector is a life-saving drug for the emergency treatment of immediate-type allergic reactions (type I). Nevertheless, it is sometimes applied incorrectly or underused because of short shelf life, high costs, fear of use, or inconvenience of carrying. FMXIN002, a nasal powder spray of epinephrine, was developed as a needle-free alternative.

OBJECTIVE: To compare epinephrine pharmacokinetics, pharmacodynamics, and safety after the administration of the FMXIN002 nasal spray versus autoinjector.

METHODS: An open-label trial was performed in 12 adults with seasonal allergic rhinitis without asthma. Epinephrine pharmacokinetics, pharmacodynamics, and safety were compared between FMXIN002 (1.6 mg and 3.2 mg) administered intranasally with/without a nasal allergen challenge and IM (0.3 mg) EpiPen.

RESULTS: FMXIN002 3.2 mg, administered after a nasal allergen challenge, displayed a shorter Tmax than EpiPen (median: 2.5 minutes vs 9.0 minutes, statistically nonsignificant [NS]) and a significantly shorter time when the measured analyte concentration is 100 pg/mL during the absorption phase pg/mL (median: 1.0 minutes vs 3.0 minutes for FMXIN002, $P < .02$). Moreover, FMXIN002 3.2 mg administered after the challenge test has resulted in a doubling of the maximal measured plasma analyte concentration over the sampling period (1110 vs 551 pg/mL, NS); area under the curve from 0 to 8 hours was 56% higher (672 vs 431 hours pg/mL, compared with EpiPen, NS). Pharmacodynamic response was comparable at all treatments. FMXIN002 was well tolerated, and treatment-emergent adverse events (AEs) were mild, local, and resolved spontaneously. No AEs were reported after the administration of EpiPen in our study. FMXIN002

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Abbreviations used
AE- Adverse event
AUC- Area under the curve
BMI- Body mass index
ECG- Electrocardiogram
FDA- Food and Drug Administration
IM- Intramuscular
IN- Intranasal
PK- Pharmacokinetics
SPT- Skin prick test
UDS- Unit dose powder device

was stable for 2 years at room temperature conditions. However, variability in the pharmacokinetics (expressed in coefficient of variation) is high. Having a prior nasal allergen challenge results in a substantial increase and speed of absorption.

CONCLUSIONS: Intranasal absorption of dry powder epinephrine is faster than EpiPen offering a clinical advantage in the short therapeutic window for the treatment of anaphylaxis. The FMXIN002 product offers a needle-free, pocket-size, safe, user-friendly, and stable alternative to epinephrine auto-injectors. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Anaphylaxis; Intranasal; Bioavailability; Epinephrine; Powder; Spray*

Epinephrine is the only life-saving drug universally recommended for the treatment of anaphylaxis, a systemic and life-threatening allergic reaction.[1,2] Global anaphylaxis incidence is reported to be 50 to 112 episodes per 100,000 person-years. The rate of recurrence of anaphylaxis in high-risk patients is estimated to be 26.5% to 54.0%.[3]

Epinephrine is currently available in an injectable dose form in ampules or autoinjectors for intramuscular (IM) administration. Nevertheless, significant underuse of epinephrine autoinjectors is reported in multiple studies and was previously reviewed.[4,5] The reasons underlying this problem include low availability in large parts of the world, difficulties in product transportation, short shelf life, high costs, fear of needle use, incorrect administration, or inconvenience of carry the large autoinjector's package, especially among teens and young adults.[5-7]

We have recently developed a novel nasal powder-based formulation of epinephrine, FMXIN002. Because of the high density of capillary beds in the nasal mucosa, intranasal (IN) administration of epinephrine could potentially result in rapid absorption and fast onset of action, thus obviating the need to use IM injection. Moreover, because of the better distribution of powder in the nasal cavity, powder nasal formulations are well known to offer quicker and higher absorption compared to liquid nasal formulations.[8] The powder formulation was designed to be administered using a small, pocket size unit dose device (Aptar Pharma, Le Vaudreuil, France), which is Food and Drug Administration (FDA) approved for another drug (glucagon nasal spray "Baqsimi" of Lilly, also in a powder format). The powder formulation can be stored in the device and kept stable at room temperature conditions for up to 2 years (available in this article's Online Repository text at www.jaci-inpractice.org). The combination of a favorable pharmacokinetic (PK) profile, extended shelf life, and patient convenience could potentially help overcome some of the obstacles associated with IM administration of epinephrine.

Herein, we aim to compare epinephrine PK, pharmacodynamics, and safety after administration by the FMXIN002 nasal spray versus IM autoinjector.

METHODS

Study participants and design

This was an open-label, 3-treatment clinical study comparing epinephrine PK in 12 adults aged 18 to 55 years (male and nonpregnant or lactating female, nonsmoking), with a body mass index (BMI) of 18-30 kg/m^2, without a history or presence of clinically significant or abnormal conditions including asthma, but with a history of allergic rhinitis.

Exclusion criteria included the presence of a medical condition requiring regular medication (prescription and/or over-the-counter) with systemic absorption other than oral contraceptives.

To ensure the safety of the trial and avoid severe anaphylactic reactions during challenge tests, subjects with asthma were also excluded from the study. The use of nasal decongestants and oral or IN steroidal or antihistamine drugs was not allowed 7 days before the study initiation and throughout the study period.

The screening procedure included allergy skin prick tests (SPTs; manufactured by ALK, Denmark) and a nasal cavity examination. SPTs were used to verify the presence of allergy and to identify the specific allergen to be used for the nasal allergen challenge.

The study consisted of 2 periods separated by 2 to 3 weeks of washout (Figure 1). On the first day of period 1 (A), the subjects received a single IM injection of EpiPen (0.3 mg).

On each of the subsequent 2 days (ie, days 2 and 3), the subjects received 1.6 mg of IN epinephrine (FMXIN002) into the right nostril without (day 2, B1) or after the nasal allergen challenge (day 3, B2). The allergen was sprayed into the right nostril in each patient. During period 2, the subjects received 1.6 mg of IN epinephrine (FMXIN002) into both nostrils (total 3.2 mg) either without (day 1, C1) or after the nasal allergen challenge into the right nostril (day 2, C2).

FMXIN002 (1.6 mg and 3.2 mg epinephrine, powder spray; Nasus Pharma, Israel) and IM epinephrine (0.3 mg) injection (EpiPen; Mylan Specialty L.P.) were administered by trained personnel after an overnight fast. Fasting was based on FDA recommendation for bioequivalence studies for inhaled epinephrine.[9] The doses were selected based on our clinical experience with the nasal powder technology, using other small molecules,[10] and on previous IN administration of liquid formulations of epinephrine.[11-13] The nasal administration using FMXIN002 is illustrated in Figure 1, *D*.

Safety assessments were performed at screening, each dosing day, and at the end of the study period. These included clinical parameters such as vital signs, as well as laboratory evaluation including hematology, chemistry, urinalysis, and 12-lead electrocardiogram (ECG). Systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and 12-lead ECG were recorded before dosing and periodically 4 hours after dosing for epinephrine pharmacodynamic response and for safety follow-up.

In addition, nasal cavity examination was performed at screening, before and after each study drug administration, and at the end of the study. The examination included evaluation by an ENT specialist and the subjects' questionnaire (available in this article's

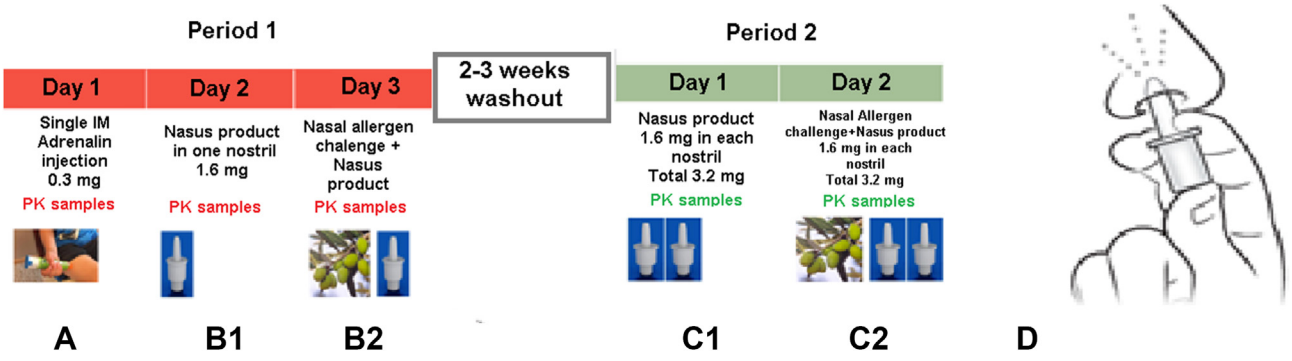

FIGURE 1. Study design consisting of 2 periods of epinephrine administration via intramuscular (IM) and intranasal (IN) routes. The 2 periods were separated by 2 to 3 weeks of washout. (**A**) On the first day of period 1, the subjects received a single IM injection of epinephrine (0.3 mg). (**B**) On each of the subsequent 2 days (ie, day 2 and day 3), the subjects received 1.6 mg of IN epinephrine (FMXIN002) in one nostril without (day 2, B1) or after a nasal allergen challenge (day 3, B2). (**C**) During period 2, the subjects received 1.6 mg of IN epinephrine (FMXIN002) in each nostril (total 3.2 mg) either without (day 1, C1) or after a nasal allergen challenge (day 2, C2). (**D**) An illustration of FMXIN002 nasal administration. *PK*, Pharmacokinetics.

Online Repository text at www.jaci-inpractice.org). The subjects did not have active rhinitis in the check-in examination. Rhinitis manifested only after the nasal allergen challenge was conducted. One subject reported temporal nasal congestion after treatment C without a nasal allergen challenge (FMXIN002 spray 3.2 mg). This was resolved spontaneously without any medication. Other subjects were without reported symptoms or abnormal findings.

Pollen and aeroallergen nasal provocation tests were performed according to Dordal et al[14] 15 to 30 minutes before treatment dosing, by IN exposure of the subject to a solution containing selected pollens and aeroallergens, which were found to be active by a documented SPT or at the screening phase (allergen solutions used: house dust mite, olive tree pollen, cypress pollen, and grass pollen mix).

Epinephrine PK was evaluated based on 21 plasma samples collected on each dosing day, including at −1, −0.5, 0 hours' sampling before dosing for endogenous epinephrine baseline measurement and at 1, 2, 3, 4, 6, 8, 10, 15, 20, 25, 30, and 45 minutes and 1, 2, 3, 4, 6, and 8 hours after epinephrine administration. To avoid stress that could lead to the elevated level of endogenous epinephrine, a peripheral venous catheter was inserted before study initiations for repeated blood draws. The blood samples were placed in ice and immediately separated by cold centrifugation (3000 revolutions per minute). The separated plasma samples were immediately frozen and stored at −70°C until analysis. Determination of epinephrine in plasma samples was done by the validated liquid chromatographic tandem mass spectrometric detection method (Pharma Medica Research Inc, Canada) in compliance with Organisation for Economic Co-operation and Development Good Laboratory Practice.[15]

Statistical analysis

Statistical analysis was performed using SAS. To account for levels of endogenous epinephrine, the measured epinephrine plasma concentration was corrected by substruction of the mean of 3 baseline epinephrine plasma concentrations obtained before dosing. Multiple comparisons between treatments were applied for PK parameters, Tmax, maximal measured plasma analyte concentration over the sampling period (Cmax), area under the curve from 0 to 0.5 hours ($AUC_{0\text{-}0.5h}$), $AUC_{0\text{-}8h}$, and time when the measured analyte concentration is 100 pg/mL during the absorption phase (T100). T100 was used as an outcome because the blood level of 100 pg/mL is considered the threshold for clinical impact. Therefore, a shorter T100min is good evidence for faster treatment of anaphylaxis.[16]

Nonparametric tests were used for time attributes. *P* values were adjusted for multiple comparisons using the Sidak method. Figures were built using GrpahPad Prism version 6.0 for Windows (GraphPad Software, San Diego, Calif; www.graphpad.com).

Ethical approval of the study

The study was performed at the phase I unit at the Hadassah Medical Center, Jerusalem, Israel. The study protocol was approved by Hadassah's institutional review board (IRB number: 0002-20-HMO), and after a detailed explanation, the participants signed an informed consent (registered: NCT04696822 clinicaltrials.gov).

FMXIN002 preparation and stability testing

FMXIN002, a new pharmaceutical composition, was manufactured by the spray-dry technique and filled into the disposable unit dose powder device (UDS; Aptar Pharma, France). The drug-device product was analyzed to control the powder particle size, drug content and purity, uniformity, microbial cleanliness, and stability. Each UDS was packed in a sealed protective pouch and contained 1.6 mg of epinephrine. The clinical batch was successfully produced in compliance with Good Manufacturing Practice. No conversion to inactive (E)-(+) epinephrine or D-epinephrine has been determined in intranasal powder product.

Stability of FMXIN002 devices was determined after storage for 6 months at 40°C ± 2°C and 75% ± 5% relative humidity (accelerated conditions) and for 24 months at 25°C ± 2°C and 60% ± 5% relative humidity (room temperature conditions).

RESULTS

Clinical study subject demographics

Three females and 9 males participated in the study. All subjects had allergic rhinitis and all of them were Caucasians. The mean (±standard deviation) age was 24.9 ± 5.9 years. The subjects' mean height, weight, and BMI were 170 ± 10 cm, 71.6 ± 10.9 kg, and 23.7 ± 3.3 kg/m^2, respectively.

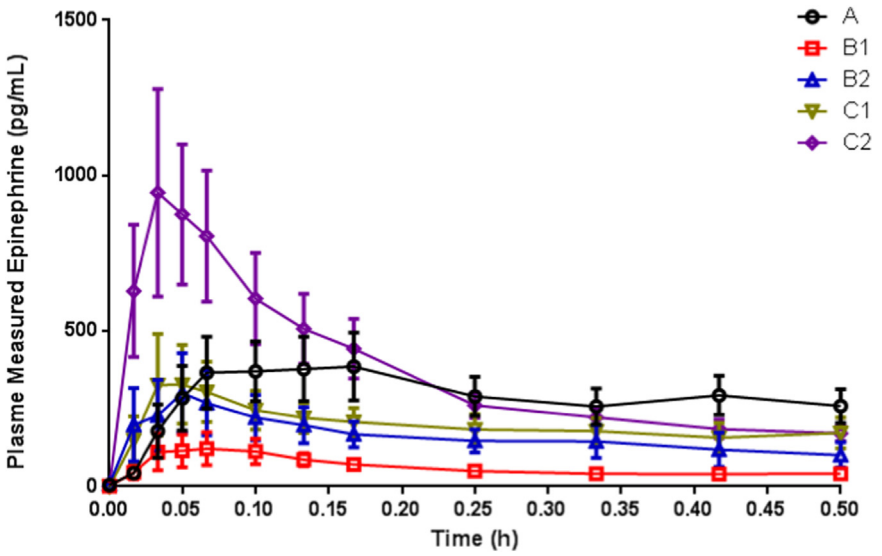

FIGURE 2. Mean plasma baseline-corrected epinephrine concentration-time profile at 30 minutes after dosing: linear scale. Results are mean + standard error.

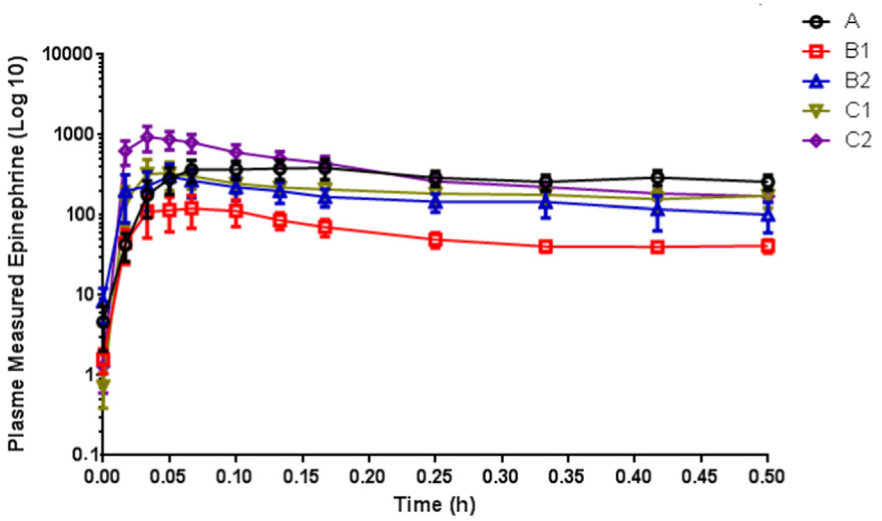

FIGURE 3. Mean plasma baseline-corrected epinephrine concentration-time profile at 8 hours after dosing: logarithmic scale. Results are mean + standard error. Data are presented in the logarithmic scale for better graphical clarity.

Pharmacokinetic effect and statistical analysis

Plots of plasma epinephrine corrected for baseline from the time of administration until 0.5 hours and from the time of administration until 8 hours after administration are shown in Figures 2 and 3, respectively. Plasma PK parameters of investigational and reference treatments are shown in Table I. Individual plasma baseline-corrected epinephrine concentration-time curves are presented in this article's Online Repository at www.jaci-inpractice.org. These data demonstrate variability between tested subjects. FMXIN002 3.2 mg (1 dose of 1.6 mg per each nostril) after the allergen challenge (treatment C2) displayed a shorter Tmax (median 2.5 minutes) as well as a significantly shorter T100 pg/mL (median 1.0 minutes, statistically significant difference compared with EpiPen, $P < .02$). The median T100 was 3.0 minutes in EpiPen, Nasus 1.6 mg + allergen challenge and Nasus 3.2 mg intervention groups. In the Nasus 1.6 mg group, median T100 was 4.5 minutes.

Furthermore, after treatment of C2 (FMXIN002 3.2 mg, after the allergen challenge), Cmax and $AUC_{0\text{-}8\ h}$ were increased in the FMXIN002 group, as compared with the IM autoinjector (1110 vs 551 pg/mL and 672 vs 431 hours pg/mL, respectively). Because of the small sample size and the interindividual variability, these differences have not reached statistical significance after adjusting for multiple comparisons using the Sidak method.

After the nasal allergen challenge test, all 12 patients developed nasal congestion, as measured by the Lebel score.[17] In both doses of IN administrations, the nasal congestion achieved after the allergen challenge resulted in a higher plasma concentration

TABLE I. Summary of bioavailability results

Attribute	EpiPen	Nasus 1.6 mg	Allergen challenge + Nasus 1.6 mg	Nasus 3.2 mg	Allergen challenge + Nasus 3.2 mg
$Tmax_{min}$, median	9.00	16.50	8.98	5.99	2.50
(rang: min-max)	(2.0-120.0)	(2.0-480.0)	(3.0-480.0)	(1.0-215.0)	(1.0-10.0)
CV (%)	166	192	179	205	83
$Cmax_{pg/mL}$, mean	550.9	196.0	322.4	447.1	1110.0
(standard error)	(99.1)	(60.6)	(89.5)	(53.0)	(313.4)
CV (%)	63	107	96	119	98
AUC $0.5h_{hr*pg/mL}$, mean	144.7	30.6	71.6	93.2	184.9
(standard error)	(26.2)	(7.4)	(19.1)	(27.5)	(37.0)
CV (%)	63	83	93	102	69
AUC $0\text{-}8h_{hr*pg/mL}$, mean	431.3	247.2	460.5	668.0	672.0
(standard error)	(49.9)	(21.3)	(97.4)	(103.2)	(86.6)
CV (%)	40	30	73	54	45
$T100_{min}$, median	3.0	4.5	3.0	3.0	1.0*
(range: min-max)	(1.0-120.0)	(1.0-60.0)	(0.020-360.0)	(0.002-45.0)	(1.00-3.0)
CV (%)	243	176	295	149	50

CV, coefficient of variation.
*Statistical significance compared with all other treatments, Sidak P value = .01936.

of epinephrine. Without the allergen challenge, the increase in the dose from 1.6 to 3.2 mg resulted in a higher than double increase in plasma concentration compared to with the allergen challenge.

Pharmacodynamic results

After all treatments, mean heart rate, systolic and diastolic blood pressure, and respiratory rate slightly increased 15 minutes after dosing and returned to baseline by 4 hours after dosing. All the measured values remained within the normal clinical range (Figure 4). There was no difference in the clinical vital signs after EpiPen injections and after Nasus IN powder in all treatments.

Safety

No serious adverse events (AEs) occurred during the study. None of the subjects withdrew from the study due to an AE. A total of 15 AEs were reported in 11 subjects (91.7%) during the study. No AEs were reported after the administration of EpiPen. Twelve events in 9 subjects (75.0%) were considered as related to the study treatment (Table II). Most events were mild.

The most common treatment-related AEs were application site erythema, which was reported in 4 subjects, headache (2 subjects), and nasal congestion (1 subject). No clinically significant changes in laboratory test values (hematology, chemistry, and urinalysis) were observed between screening and the end of the study. No clinically significant abnormal findings were noted in physical examination, vital signs, or ECG results.

FMXIN002 stability

FMXIN002 powder in the devices was stable after storage for 6 months at 40°C ± 2°C and 75% ± 5% relative humidity (accelerated conditions) and for 2 years at 25°C ± 2°C and 60% ± 5% relative humidity (room temperature data are available in this article's Online Repository text at www.jaci-inpractice.org). In that regard, the new nasal spray has a significant advantage over EpiPen; the nasal spray is stable in room temperature for at least 24 months, in comparison with 12 to 18 months, for EpiPen.

DISCUSSION

FMXIN002, an IN powder formulation of epinephrine, was found to be safe and well tolerated. Compared with the conventional IM epinephrine, FMXIN002 exhibits faster absorption as reflected by a shorter Tmax and significantly quicker time to reach clinical effective plasma concentrations. The simple administration method that does not require IM injection represents a potential advantage for the treatment of allergic emergency conditions, such as anaphylaxis, over the current IM therapeutic approach. In addition, as the IN administration of the FMXIN002 product is not painful and does not include injection into a tissue, we believe that patients' compliance with epinephrine administration will increase.

The administration of IN epinephrine was previously studied in canine models.[18-20] In one study, an IN histamine challenge of 12 dogs was followed by IN epinephrine with a significant reduction of nasal congestion compared with IN saline.[18] Another study evaluated the PK characteristics of IN epinephrine in dogs and found significantly increased plasma absorption without an increase in heart rate, as compared with IM epinephrine administration.[19] Human studies have further supported the notion of bioequivalence of IN versus IM administration of epinephrine.[11,12] This corresponds with another study demonstrating equivalent plasma epinephrine levels after the IN administration of 5 mg of epinephrine and IM 0.3 mg, as well as increased levels of IN epinephrine, as compared with IN saline.[13] Thus, these studies suggest that the development of a commercial IN epinephrine product is plausible.

Several IN solution-based epinephrine products are currently under clinical development.[21,22] The characteristics of dose, mode of delivery, and PK in the different IN epinephrine products are detailed in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). Comparison between powder- versus water-soluble liquid-based products, as well as the specific mechanism of the FMXIN002 product, reveals that the FMXIN002 product is better distributed in the nasal cavity and reaches more efficiently the optimal absorbing

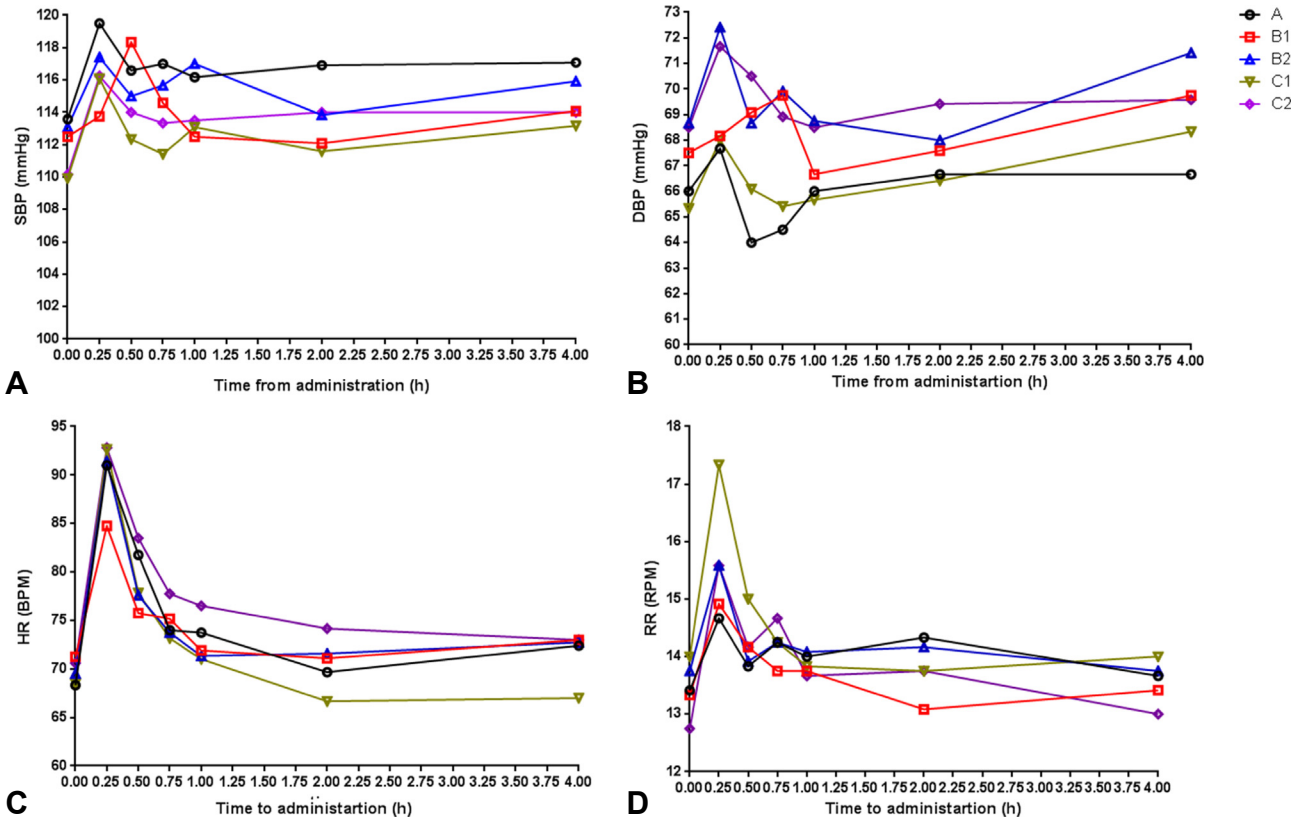

FIGURE 4. Pharmacodynamic parameters: (**A**) systolic blood pressure (SBP), (**B**) diastolic blood pressure (DBP), (**C**) heart rate (HR), (**D**) respiratory rate (RR). All results are presented as means. There were no significant differences compared with EpiPen. All results were within normal clinical ranges. (Standard error is not presented for graphical clarity.) *BPM*, Beats per minute; *RPM*, respirations per minute.

area of the mucosa, which is located above the bulbar region. This even distribution and the powder unique molecular structure allow a more efficient absorption of epinephrine to the plasma, as compared with solution-based products. Furthermore, unlike solution-based formulations and due to the unique powder particle's structure, no absorption enhancers are required to facilitate significant plasma levels of endogenous epinephrine and no stabilizers are needed to ensure the product shelf life.

This is supported by different studies. Djupesland et al[23] have shown by dynamic gamma camera imaging that the distribution of powder nasal spray achieved significantly larger initial deposition in the upper and middle posterior regions of the nose than liquid spray. Furthermore, we have recently shown in a clinical trial with another molecule, using the same technology, that dry powder spray achieved higher blood absorption in comparison with liquid nasal spray.[10] The unique molecular structure, patent granted, was studied by scanning electronic microscopy and elemental analysis.[24]

The inherent advantage of improved bioavailability by using powder nasal drug delivery has been described extensively in the literature.[25,26,27] Liquid-based nasal formulations are characterized by variable absorption rates because a large fraction of the sprayed drug is deposited in the lower anterior segment of the nasal cavity in front of the nasal valve.[23] This is an anatomical site lined with nonciliated squamous epithelium that is less permeable to drugs than the respiratory mucosa beyond the nasal valve.[27] It has been reported that powder-based IN formulations may reach the blood stream faster and have better bioavailability than liquid sprays due to significantly larger deposition in the nasal mucosa. This phenomenon was recently reaffirmed by our group testing powder versus liquid nasal formulation of naloxone, demonstrating quicker and higher drug absorption for the emergency treatment of opioid overdose.[11]

Vital signs, including systolic and diastolic blood pressure, and respiratory rate slightly increased 15 minutes after dosing at all treatments (IN sprays and EpiPen) and returned to baseline by 4 hours after dosing. However, no significant differences, as compared with EpiPen, were observed. Moreover, all results were within normal clinical ranges. We speculate that the observed small differences may be due to response to the act of injection.

In the current trial, beyond the PK and pharmacodynamic measurements, the team has noted immediate disappearance of nasal allergy symptoms at treatments B2 and C2 (FMXIN002 given after the allergen challenge), suggesting a fast clinical influence of epinephrine after the nasal powder administration. For comparison, allergy symptoms in allergic subjects after nasal provocation are reported to last at least 30 minutes.[28,29] However, the systemic effects of nasal epinephrine administration, as in the case of anaphylaxis, were not directly evaluated and are not necessarily reflected by these results. Thus, conclusions must be drawn carefully. This clinical impression of a fast response should be accurately measured at the next clinical trial.

In the current study, we observed nonlinear proportion between the nasal dose and Cmax and AUC values, as the increase

TABLE II. Summary of treatment-related AEs by the MedDRA system organ class and preferred term

	FMXIN002 1.6 mg		FMXIN002 3.2 mg		
	No nasal allergen challenges (n = 12)	Nasal allergen challenges (n = 12)	No nasal allergen challenges (n = 12)	Nasal allergen challenges (n = 12)	All (n = 12)
MedDRA system organ class/preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 treatment-related AE*	2 (16.7)	2 (16.7)	4 (33.3)	3 (25.0)	9 (75.0)
General disorders and administration site conditions					
Application site erythema	2 (16.7)	0 (0)	2 (16.7)	0 (0)	4 (33.3)
Nervous system disorders					
Headache	0 (0)	0 (0)	2 (16.7)	1 (8.3)	3 (25.0)
Respiratory, thoracic, and mediastinal disorders					
Nasal congestion	0 (0)	1 (8.3)	1 (8.3)	2 (16.7)	3 (25.0)
Rhinitis allergic	0 (0)	0 (0)	0 (0)	1 (8.3)	1 (8.3)

AE, Adverse events
*Possibly or likely related.

in Cmax and AUC from 1.6 mg to 3.2 mg is more than doubled. We also observed a significant increase in epinephrine nasal absorption to the blood after nasal congestion achieved by allergen nasal provocation. This phenomenon is not surprising because allergic rhinitis response involves weakening of the nasal epithelial barrier due to reduced expression of tight junction mRNA and proteins, as reviewed by Nur Husna et al.[30] A similar trend of increased nasal absorption of epinephrine under the nasal congestion condition had been observed formerly by other groups in human[31] and canine studies.[18]) The extent of variability in the PK results of all treatments was rather high, expressed by coefficient of variation (CV%) values (Table I). High variability was also found in former PK studies with epinephrine IM injections.[32,33.] Epinephrine is known as a highly variable drug, as was reported earlier for autoinjectors[25] and lately for liquid nasal spray.[34] This high variability will be considered in our future studies, according to the reference-scaled average bioequivalence approach.[35]

Besides the favorable PK, FMXIN002 has practical advantages over current treatment options because it is stable at room temperature for at least 2 years and easy for storage and transport. FMXIN002 IN needle-free epinephrine may overcome the obstacles of administration technique difficulties, low compliance, post-traumatic effect, difficulties in global distribution, and high market costs of current epinephrine injectors. The advantages of a user-friendly, pocket-size device are of particular importance to teenagers with allergies who are at risk for severe and fatal reactions but tend to avoid carrying autoinjectors as prescribed due to inconvenient packaging.[36]

Future studies are planned in accordance with the regulators' instructions. Not all patients with anaphylaxis experience nasal congestion. Moreover, a varying degree of rhinitis or nasal mucosal barrier dysfunction might impact the IN epinephrine uptake. Hence, we intend to continue additional studies in larger groups and to slightly increase the dose to 4 mg, thus supporting all the potential patients and complying with regulators' instructions. Exact dosing is controlled in our product. Thus, in future studies, we intend to optimize the dose in a single UDS, for example, 3.2 mg or 4 mg in a single UDS.

Furthermore, our trial did not evaluate the efficacy of IN epinephrine delivery in special populations, such as obese and pediatric patients. In obese, there are concerns regarding increased skin-to-muscle distances with different drug delivery results between Epipen autoinjectors and IM manual administration.[37] In children, there is a risk of intraosseous administration, while attempting IM injection, due to inappropriate needle size.[38] Thus, we believe that IN administration of epinephrine may be beneficial, in that regard, in both populations.

In addition, this study points to potential downsides of IN dry powder epinephrine because of possible higher variability among patients. Therefore, we intend to perform additional trials in larger populations and with slightly higher dose to research this question and to offer an affective level of epinephrine to all patients. Because some patients will not have nasal congestion during anaphylaxis, it is necessary to achieve the adequate level of epinephrine in the blood using IN spray, without an allergenic challenge. We believe that this goal will be addressed in our next clinical trial.

Our study has several limitations. The number of participants is relatively small, and the study population skewed toward male subjects due to difficulties in recruiting female subjects to the trial. Furthermore, the study population consisted of healthy volunteers. Subjects with asthma, anaphylactic reactions, or shock, as well as specific populations, such as obese, pediatric, and elderly patients, were not included. Thus, conclusions from our study should be drawn while taking these into account, and further studies concerning these issues are needed.

In conclusion, introduction of FMXIN002, an IN powder formulation of epinephrine, appears to be safe and effective. Usage of IN epinephrine will allow us to simplify administration of adrenalin, avoid pain and injection into a tissue, and increase compliance of self-treatment by the patients. Thus, it holds a potential to promote self-administration of adrenalin in early stages of anaphylaxis. The encouraging findings obtained in the present study should be substantiated in a larger clinical study. Faster absorption of epinephrine after the IN administration of FMXIN002, if confirmed, clearly represents a potential advantage over the currently available treatment modality for allergic reactions including anaphylaxis.

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