A new fast-acting naloxone powder nasal spray for opioid overdose

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Introduction

Naloxone hydrochloride is the opioid antagonist most commonly used for the complete or partial reversal of opioid overdose, including respiratory depression, sedation, and hypotension. Intranasal (IN) administration is quick, non-invasive and easy to use, as compared to parenteral injection, and protects against accidental intra-vessel injection. The current on the market Intranasal naloxone are liquid formulations. The liquid-based delivery systems, suffer from variable absorption owing to a large fraction of the delivered drug being deposited in the lower anterior segment of the nasal cavity, predominantly lined with non-ciliated squamous epithelium that is less permeable to drugs than the respiratory mucosa beyond the nasal valve. Powder-based intranasal formulations may reach the blood stream faster and have better bioavailability than liquid sprays due to significantly larger deposition in the nasal mucosa[1]. Nasus Pharma developed FMXIN001, a new dry powder-based delivery system and compared its bioavailability and safety to NARCAN® liquid Nasal Spray in two clinical trials.

Aims

Clinical pharmacokinetics and safety assessment of a new intranasal powder-based naloxone formulation for the treatment of opioid overdose

Methods

FMXIN001, was developed by blending drug microspheres produced by spray-drying with larger lactose monohydrate particles, that serve as excipient. The powder was fully characterized to control the chemical composition and particle size distribution, and then filled into Unit dose Devices (UDS, Aptar, France) forming ready to use drug-device products.

Clinical studies: We compared the pharmacokinetics and safety of FMXIN001 versus NARCAN® in a pilot study with 14 healthy adults followed by a pivotal trial in 42 healthy adults (NCT04713709). Total, 56 healthy female and man, age 18-64 participated. The studies were open-label, single-dose, randomized, two-period, two-treatment, two-sequence crossover studies to assess the pharmacokinetics and safety of FMXIN001 versus NARCAN® liquid nasal spray. 17 blood samples were collected in each period for analysis of unconjugated naloxone in plasma by a LC-MS/MS method, which had been validated over a calibration range of 0.0100 - 15.0 (ng/mL).

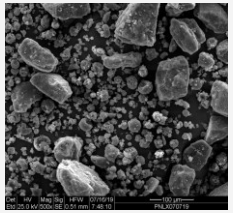
Safety monitoring included temperature, vital signs, ECG and blood pressure pre-dose, and at 1, 2, 4 and 12 hours post-dose, nasal cavity examination and questionnaires regarding nasal and non-nasal irritation. A 4-item smell test was conducted at each check-in and at the end-of-study as a marker for nasal function.

Safety study in Dogs: The safety was also assessed in a GLP-Compliant 14-Day Repeated Dose Toxicity Study of FMXIN001 Administered via Intranasal Instillation in Beagle Dogs. The test and vehicle control items were administered to groups of dogs daily by intranasal administration using Aptar Unidose (UDS) systems as described in the table below:

Group No.	Group Designation	Total Powder Dose (mg/animal)	Number of Sprayers (20 mg /spray)	Total Dose of FMXIN001 Powder (mg/kg/day) [c]	Number of Animals			
					Main		Recovery	
					M	F	M	F
1	Control	0	0	0	3	3	2	2
2	Vehicle Control	80	4 (2/NOS)	0	3	3	2	2
3	Low Dose	20	1 (right NOS)	2.5	3	3	-	-
4	High Dose	80	4 (2/NOS)	10	3	3	2	2

Study endpoints included clinical observations, detailed examinations, body weight, food consumption, ophthalmology, toxicokinetic (TK) profile (Days 1 and 14), organ weights, macroscopic examination, and histopathological examinations of the nasal cavities (4 sections) and associated lymph nodes, respiratory tract (extended tissue list including lungs, trachea, carina, larynx, nasopharynx, pharynx), brain, heart, kidneys, liver, esophagus, and stomach.

FMXIN001 Powder



Scanning Electron Microscope image of FMXIN001 powder-based formulation Demonstrating large lactose particles mixed with spheric naloxone particles.
less than 4.9% v/v of the particles are smaller than 5 µm, in order to avoid lung inhaling of the powder.

Clinical Trials Results

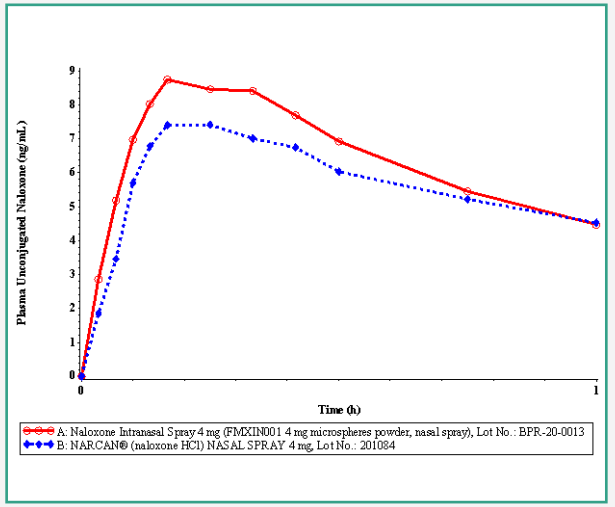
Pharmacokinetics: In human subjects (total, 56 healthy female and man, age 18-64), FMXIN001 powder spray produced significantly higher level of naloxone in the plasma at the initial time points of 4, 10, and 30 minutes, post-administration, compared to the liquid spray Narcan© . A significant treatment effect was detected by ANOVA in the analysis of C_{max} (p=0.0368), $AUC_{0\text{-}4min}$ (p=0.0058), $AUC_{0\text{-}10min}$ (p=0.0478), and $AUC_{10\text{-}30min}$ (p=0.0113).

FMXIN001 powder spray results in similar overall exposure and T_{max} to the liquid spray, but demonstrated higher absorption in the first 30 minutes, the critical therapeutic time window for treatment of opioid overdose

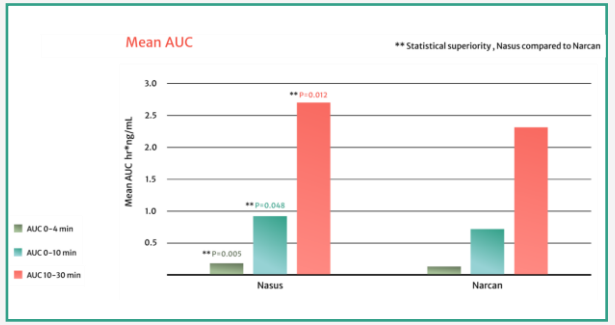
Summary of Pivotal Clinical Study Results Based on Plasma Unconjugated Naloxone Levels

Variable	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Ratio (%)	90% Confidence Interval
AUC_t	A	42	13.6021 (33)	13.0188	100.32	94.38 - 106.63
(hr*ng/mL)	B	42	13.7503 (38)	12.9777		
AUC_{inf}	A	42	13.8286 (33)	13.2355	100.35	94.49 - 106.57
(hr*ng/mL)	B	42	13.9849 (38)	13.1897		
C_{max}	A	42	10.1262 (42)	9.3761	113.01	102.73 - 124.32
(ng/mL)	B	42	8.7238 (32)	8.2965		
$AUC_{0\text{-}4min}$	A	42	0.1824 (88)	0.1159	163.22	122.98 - 216.62
(hr*ng/mL)	B	42	0.1207 (86)	0.0710		
$AUC_{0\text{-}10min}$	A	42	0.9159 (67)	0.7306	125.34	104.04 - 151.02
(hr*ng/mL)	B	42	0.7184 (57)	0.5828		
$AUC_{10\text{-}30min}$	A	42	2.6958 (37)	2.5344	113.52	104.74 - 123.04
(hr*ng/mL)	B	42	2.3211 (27)	2.2325		
Treatment A (Test)	FMXIN001 4 mg microspheres powder (Nasus Pharma, Israel)					
Treatment B (Reference)	NARCAN® (naloxone HCl) NASAL SPRAY 4 mg, (Adapt Pharma, Inc., USA)					

Mean plasma unconjugated naloxone concentration-time profile of the therapeutic window of first 1 hour (A: n = 42 / B: n = 42).



Mean AUC at first 30 minutes of the therapeutic window is significantly higher



Safety: Both treatment and reference product were well tolerated with no significant adverse events and few mild self-resolving side effects, with similar frequency between treatment and reference groups; 41.3% occurred following administration of treatment A, and 37.0% occurred following administration of treatment B. All TEAEs were mild in severity and resolved prior to end-of-study without intervention. Most mild AEs were related to nasal mucosal congestion and there were no safety concerns with regards to smell tests.

Pivotal trial: Summary of Drug-Related Adverse Events for Each Treatment

	Reported Incidence by Treatment Group n (%) of Subjects		
	A N = 46	B N = 43	Total N = 46
Subjects with Drug-Related AEs	17 (37.0%)	13 (30.2%)	24 (52.2%)
Subjects with No Drug-Related AEs	29 (63.0%)	30 (69.8%)	22 (47.8%)
Severity			
Mild	**17 (37.0%)**	**13 (30.2%)**	**24 (52.2%)**
Moderate	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)

Treatment A: FMXIN001 4 mg microspheres powder (Nasus Pharma, Israel)
Treatment B: NARCAN® (naloxone HCl) NASAL SPRAY 4 mg, (Adapt Pharma, Inc., USA)

Results of Safety Study in Dogs

Repeat daily intranasal administration of FMXIN001 with the UDS device for 14 consecutive days in dogs was well tolerated in both sexes with no mortality at any dose levels. No FMXIN001-related clinical signs, or effects on body weight, food consumption, ophthalmology parameters, organ weights, or macroscopic and microscopic examinations were noted in any groups. A mild epithelial ulcer was observed in the nasal cavity at level 1 (nasal cavity at the level of upper incisors) in one animal treated at 10 mg/kg/day (2 mg/kg/day naloxone) of FMXIN001 powder, but the change was considered incidental by the Study Director.

On Day 1, mean Cmax ranged from 19.5 to 38.9 ng/mL at 2.5 mg/kg/day and 59.5 to 60.8 ng/mL at 10 mg/kg/day, with Tmax values between approximately 0.25 to 0.58 Mean estimated t1/2 ranged from 0.581 to 0.670 hours.
Day 14 TK data was not significantly impacted compared to Day 1 indicating no significant accumulation and/or change in profile over repeated administrations. There were no major, or consistent sex-related differences for all measured TK parameters

The safety margins for human, were approximately 15.4-fold compared to the standard therapeutic dose.

Conclusions

- FMXIN001, a new intranasal powder naloxone, was safe in human and dog studies.
- FMXIN001 has shorter onset of action in the immediate and critical time window, first 30 minutes, for therapeutic intervention for opioid overdose.
- Rapid user friendly and non-invasive administration of Naloxone via nasal delivery, coupled with immediate blood absorption of naloxone in cases of opioid overdose are imperative, given the alarming increase in mortality rates.

Contact information

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Reference:

1. Djupesland, Per Gisle, and Arne Skretting. *Journal of aerosol medicine and pulmonary drug delivery* 25.5 (2012): 280-289.