NASAL INNOVATION FORUM

Harro Höfliger
ALL YOU NEED

Current and Future Nasal Pipeline: Benefits and Challenges in Drug Repurposing

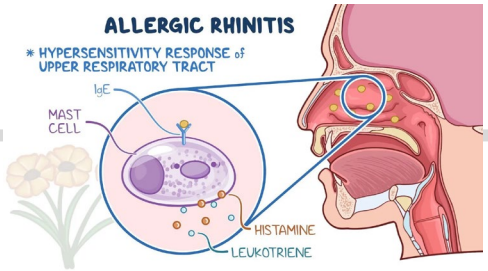
Irene Rossi, PhD |NIF 2025
September 18-19, 2025 – TCC, NJ, USA

01

NASAL PIPELINE

Nasal Delivery Market Development

Harro Höfliger
ALL YOU NEED



1996

First Launch
Imigran

Zomig, Instanyl, Narcan (2016)

2018

2020

Valtoco, Tosymra, Spravato, Nayzilam, Baqsimi

Atzumi™
(dihydroergotamine)
nasal powder

Opvee, Kloxxado, Naloxone, Zavzpret, Atzumi

TODAY

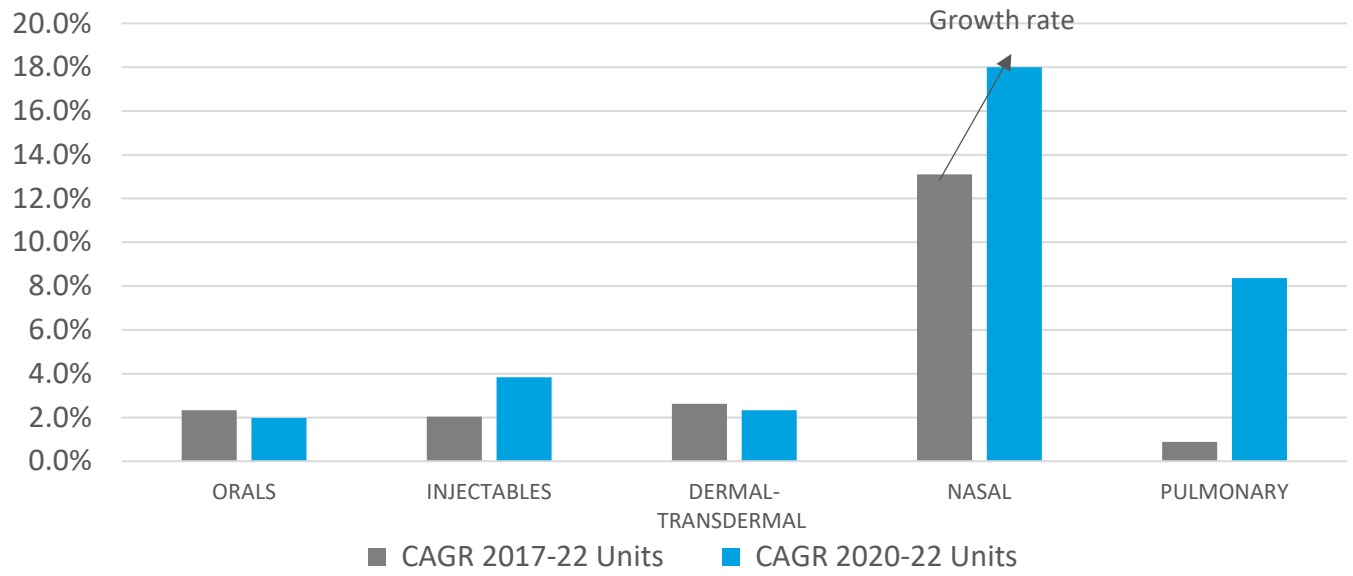
Slide Modified from Aptar Pharma's

Nasal Delivery Route Growth

- Nasal Delivery is still a niche but very fast growing, especially after Covid
- Intranasal products have a faster growth than other delivery routes
- Revenues CAGR for nasal was 29% compared to 2% CAGR for oral & 4% of injectables

  Total Nasal Rev $2B

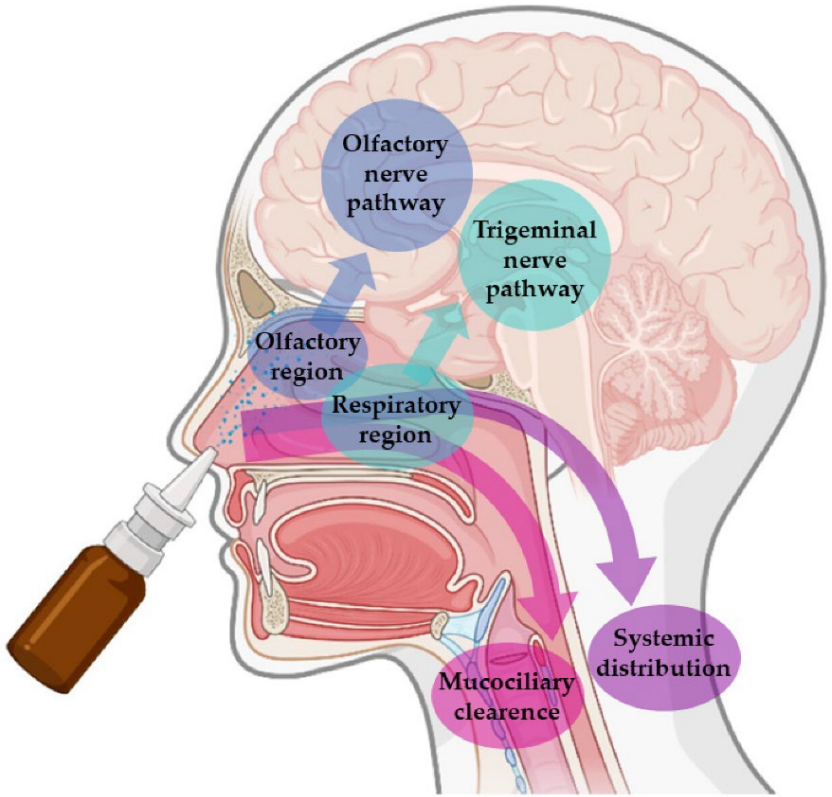
  Total Injectable Rev $41B



Slide Courtesy of Aptar Pharma

Intranasal delivery

Harro Höfliger
ALL YOU NEED



ADVANTAGES

- ❑ Improved efficacy
- ❑ Non-invasive route
- ❑ Easy administration
- ❑ By-pass hepatic first pass metabolism
- ❑ Reduced off-target effects
- ❑ Faster onset of action
- ❑ Treating various diseases
- ❑ Localized action
- ❑ Direct delivery to the brain
- ❑ Systemic delivery
- ❑ Vaccination

Tai J et al., Pharmaceutics 2022, 14, 1073 https://doi.org/10.3390/pharmaceutics14051073
Keller L et al., Drug Delivery and Translational Research 2022 12:735-757 https://doi.org/10.1007/s13346-020-00891-5

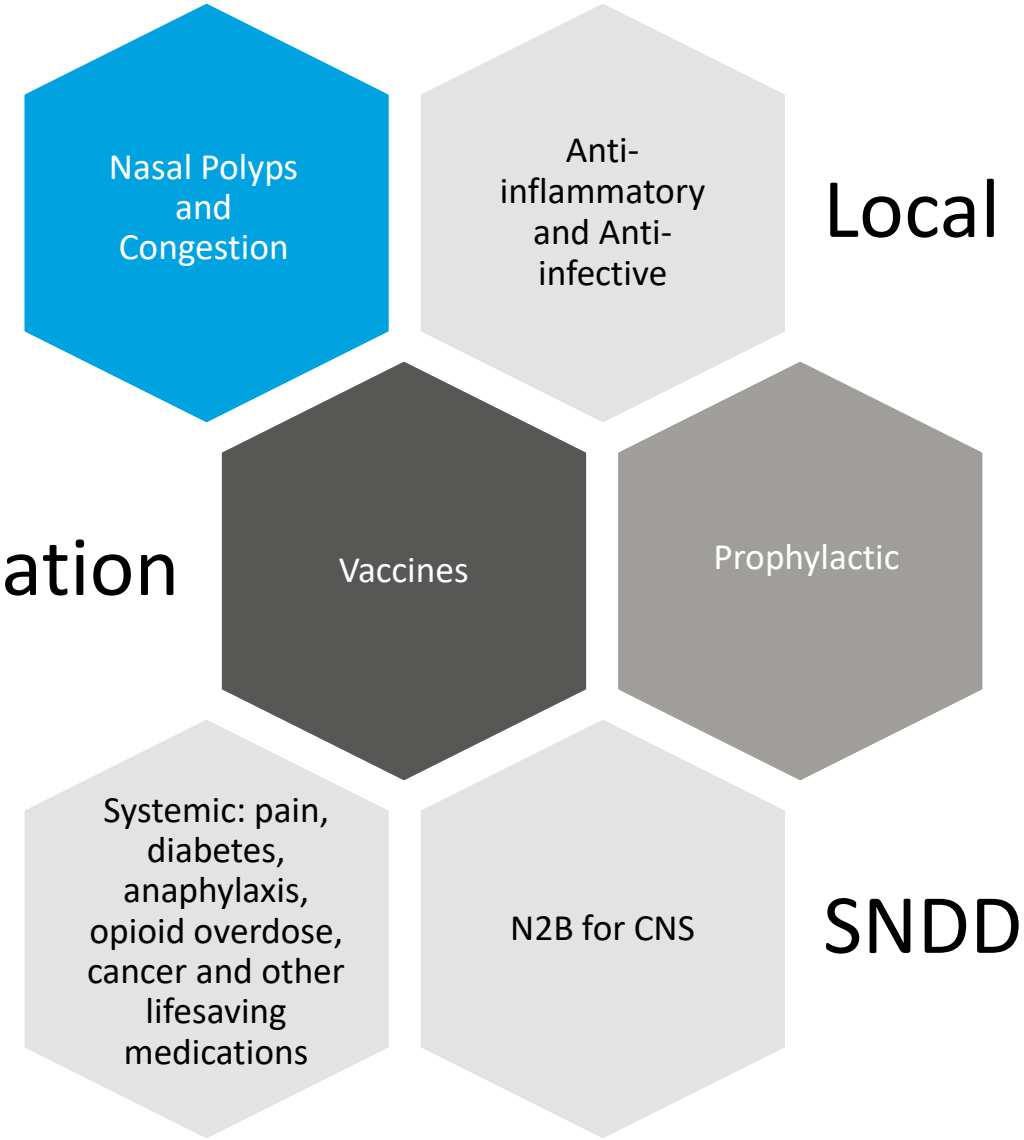
Nasal Powders VS Nasal Liquids

Harro Höfliger
ALL YOU NEED

	Powder	Liquid
Stability	Longer shelf life and stability at room temperature. No incompatibility issues between active/excipients and CCS components.	Shorter shelf life (cold chain). Assessment of active/excipients compatibility and adsorption/interaction with CCS components.
Preservative	No preservatives required.	Preservatives (unless preservatives-free device is employed. However, they require sterile filling)
Dose	Higher dose can be administered (wider dose range)	Dose limitations (max recommended volume of 0.5 mL/nostril)
Multi-Dose	Multi-dose devices under development (prototypes)	Several established multi-dose devices available
Manufacturing	More complex manufacturing process development (e.g. spray drying). Early assessment of powder processing for dosing.	Single or dual step formulation manufacturing
Solubility	More suitable for poorly water-soluble drugs and sensitive molecules (biopharmaceutics)	Solubility and long-term stability may be a challenge
Dissolution	Drug release test to be performed, especially if formulation matrix employed	Control pH and Osmolality through use of buffered systems. Formulation ready for absorption
Bioavailability	Mucociliary clearance slower (prolonged residence time). Reported higher targeted delivery and systemic bioavailability	Studies report lower bioavailability compared to powder formulations
Market	Less products on the market and patient tolerability less known	Most common for nasal products on the market (patient acceptance)

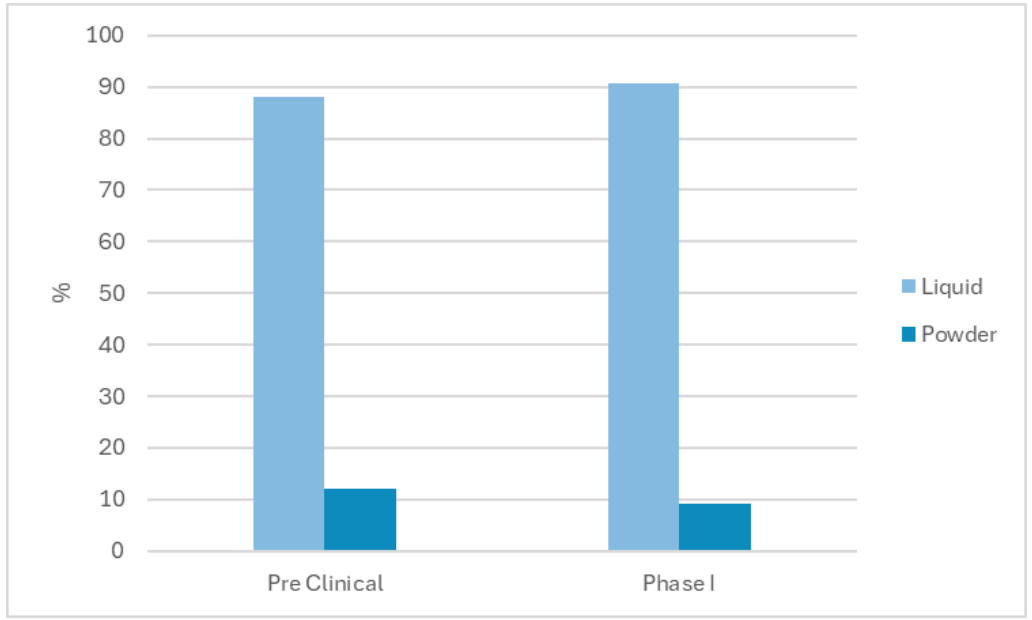
NASAL Rx PIPELINE

Harro Höfliger
ALL YOU NEED



Source PharmaCircle September 2025

Powder vs Liquid - Pipeline



- Liquid is still the preferred initial pharmaceutical form to explore nasal delivery for NCE, biologics and repurposing
- Even though Nasal Powders are still a niche of a niche the number of early development programs have been increasing exponentially over the past few years
- With recent approval we can expect more and more companies exploring nasal delivery and, potentially, starting directly the development in a powder form
- Vaccination (50% of preclinical pipeline) and CNS treatment (30% of preclinical pipeline) are leading the way followed by Cancer treatment and Pain Management

Source PharmaCircle 2025

02

DRUG REPURPOSING

The Value in Drug Repurposing: The case of IN Glucagon

Harro Höfliger
ALL YOU NEED

Ease of Administration – Patients First

- **Injection Kit**: hard to assemble, multi-steps
- **Intranasal Powder**: ready to be used by patient or caregiver, no refrigeration and portable

Injection Kit

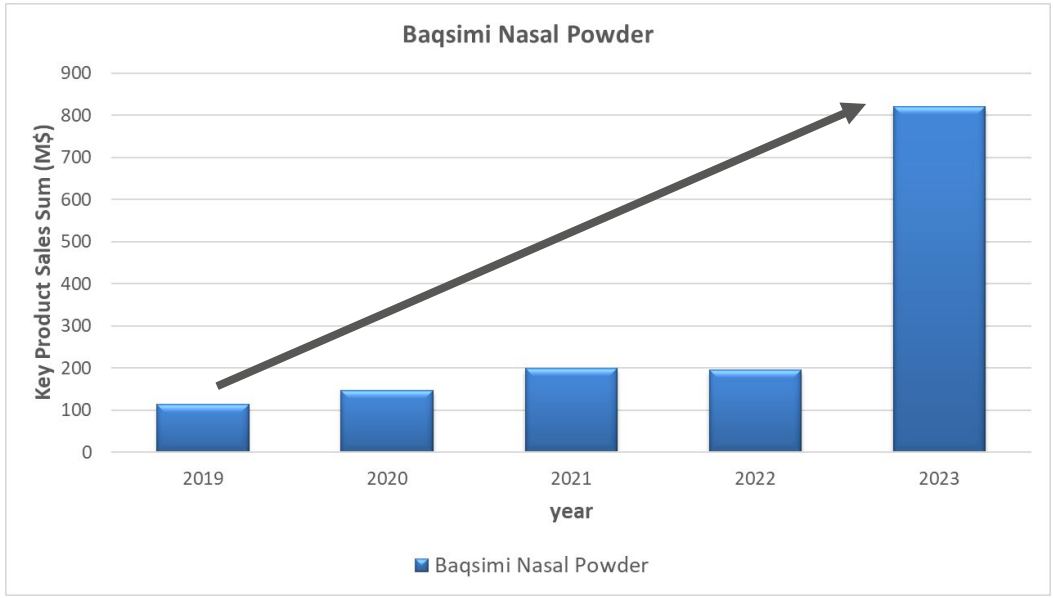
2019

Intranasal Powder

Controlled randomized studies showed they are equally effective in resolution of Hypoglycaemia

Mean costs were $992 lower if IN Glucagon was used compared with Injectable version per Severe Hypoglycaemia Events for which a user attempted treatment

BAQSIMI: The #1 prescribed glucagon in the US[1,*]
*Based on number of new prescriptions and total prescriptions in the glucagon product class, beginning February 2021 through present.

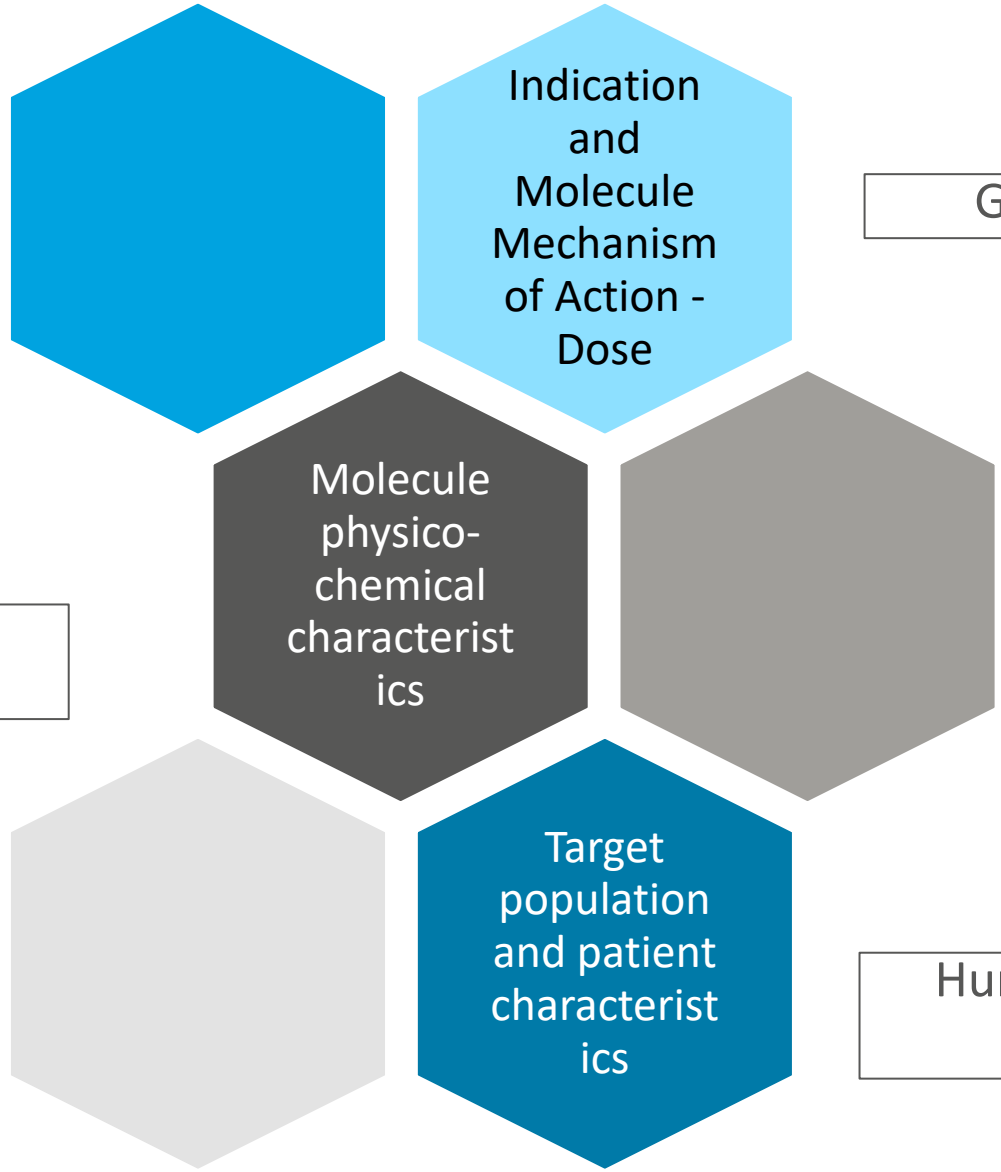


Source PharmaCircle & https://www.baqsimi.com/

Acta Diabetol. 2020; 57(6):743-749; doi: 10.1007/s00592-020-01483-y. J Diabetes Sci and Technol 2019; 13(5): 910-918; doi: 10.1177/1932296819826577.

What to take into consideration

Harro Höfliger
ALL YOU NEED



Go – No Go

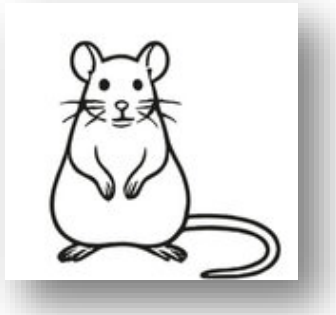
Shorten Application Process: 505b(2)

Formulation & Device Screening and Selection

Human Factors and Useability

Roadmap for Development of Repurposed Molecules

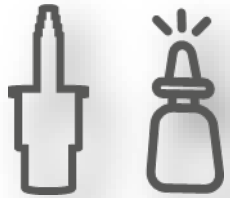
Harro Höfliger
ALL YOU NEED



- Efficacy
- Safety

Formulation Development and *In Vitro* Device Screening → Short Stability Study to Identify Lead Candidates → Preclinical Study → Manufacturing Process Optimization and Scale-up → Clinical

- Definition of the Formulation Platform
- Best Formulation-Device Combination
- Manufacturing process for Primary and Secondary Packaging



03

CASE STUDY

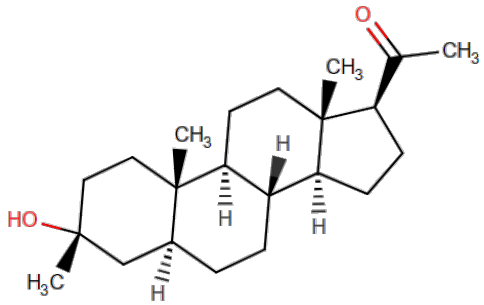
Ganaxolone

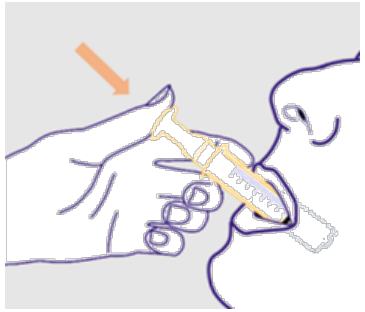
Cas n° – 38398-32-2
Chemical Formula – $C_{22}H_{36}O_2$
Molecular Weight – 332.528 g/mol
Drug Class – Neurosteroid

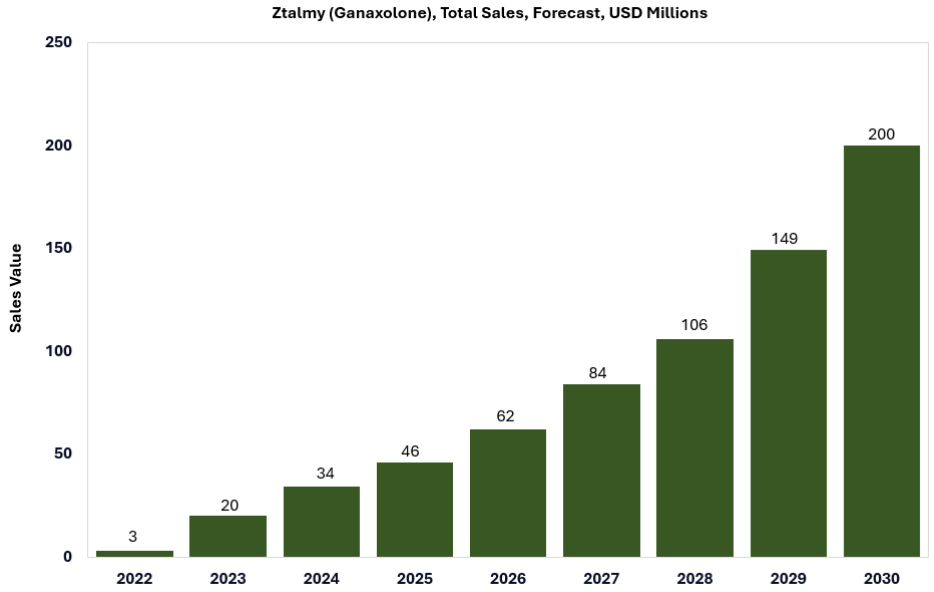
Company – Marinus Pharmaceuticals
Brand – Ztalmy®
FDA Approval – March 2022
EMA Approval – Jul 2023

Therapeutic Area – SNC
Indication – Seizures (associated with CDKL5 deficiency disorders)
Route of Adm – Oral
Dosage Form – Suspension
Dosage Strength – 50 mg/mL
Target Patients – 2 years of age and older
Standard Regimen
Week 1 450 mg/day
Week 2 900 mg/day
Week 3 1350 mg/day
Maintenance 1800 mg/day

Market Value 2023 - 20 USD mln
Market Value 2024 – 34 USD mln
Forecast 2030 – 200 USD mln







February 11, 2025
Immedica Pharma (Sweden), a leading global rare disease company, announced the completion of the acquisition of Marinus Pharmaceuticals

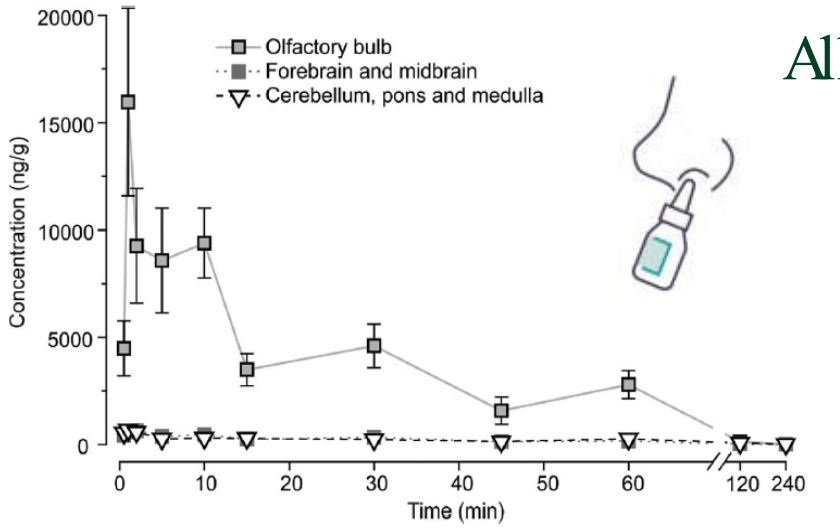
ZTALMY® (ganaxolone) CV Official Site | Home

Ganaxolone: Bioavailability and Brain Exposure

FEATURE	ORAL GNX	INTRAVENOUS GNX	INTRAMUSCULAR GNX
Market status	Commercial (Ztalmy)	Phase 3 RAISE trial did not achieve the statistical significance in patients progressing to anaesthesia after 36 h[5]	In vivo animal studies
Bioavailability	~ 10 %[1]	100% assured by definition	>95 % (3 mg/kg dose)[11]
Plasma Concentration	> 100 ng/mL in the plasma (600 mg TID)[2] T_{max} 2-3 h[1]	dose and duration dependent C_{max} 1000 ng/mL (30 mg over 5 minutes)[6]	C_{max} 550 ng/mL (3 mg/kg dose, T_{max} 2 min)[11]
Brain Exposure	n/a	n/a	C_{max} 1239 ng/g (3 mg/kg dose, T_{max} 10 min)[11] Exposure brain/plasma ratio 3:1[11]
Half-life	7.8 – 10.1 h in plasma[3]	4.6 h in plasma[7]	3.3 h in plasma, 2.6 h in brain[7]
Efficacy	Effective in seizures control (FDA-approved)	Status epilepticus cessation in 5 minutes[8]	terminated behavioral clonic seizure activity in 75% treated animals[11]
Pediatric Studies	Effective and safe for neonatal seizure[4]	Effective in terminate status epilepticus[9] 86.4% seizures reduction in lambs than phenobarbital[10]	n/a

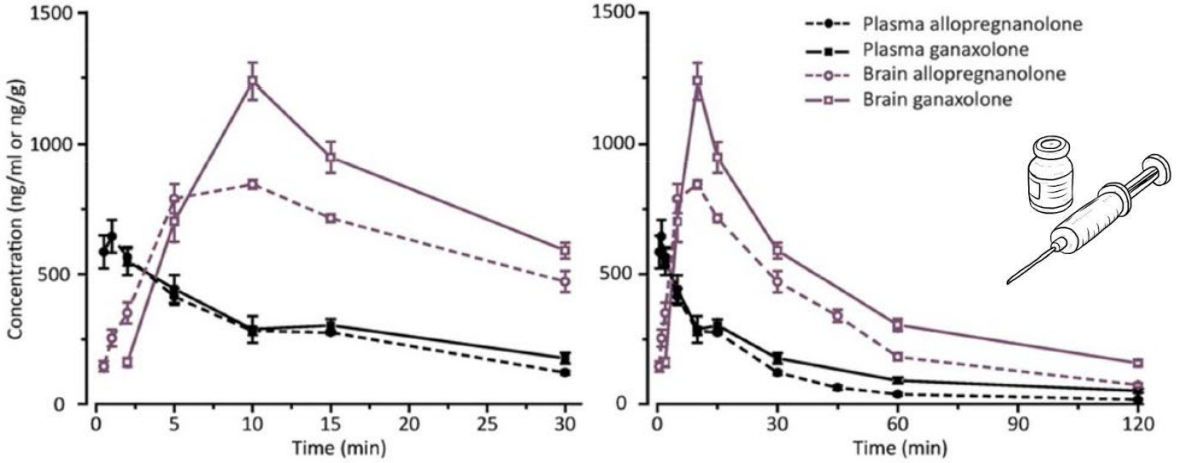
[1] Surya K. De Current Medicinal Chemistry 2024
[2] Hulihan et al. American Epilepsy Society 2020
[3] European Medicines Agency (EMA) website https://www.ema.europa.eu/en/medicines/human/EPAR/ztalmy
[4] Yawno T. Frontiers in Cellular Neurosciences 2017
[5] NCT04391569
[6] Gasior M. et al. Clinical Pharmacology in Drug Development 2024
[7] Patent no. US10172870B2
[8] Vaitkevicius H. et al. Epilpsia 2022[9] Singh RK. et al. Epilepsy & Behaviour Reports 2022
[10] Miller SL. et al. Annals of Neurology 2022
[11] Zolkowska D. et al. Epilepsia 2018

Ganaxolone: State of the Art



Allopregnanolone

- Rapid onset of action when nasally administered (< 5 min)
- Concentrated faster in the brain when IN (10 mg/Kg) compared to IM administration
- Less side effects (motor impairment) compared to benzodiazepines (hypothesis of direct N2B route vs systemic route for benzodiazepine)



Although Allopregnanolone terminated behavioural clonic seizure activity in 92% of animals vs 75% for Ganaxolone, comparable plasma levels were achieved by the two steroids

Ganaxolone (synthetic version) reported greater peak brain concentration and brain exposure (AUC) showing greater metabolic stability

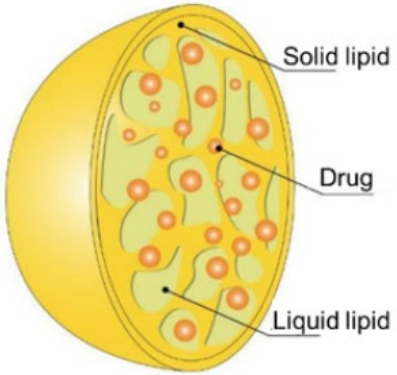
An IM dose of 3 mg/Kg of the two steroids showed 3-fold higher brain than plasma exposure

Zolkowska D. et al., Neurotherapeutics 2021
Zolkowska D. et al. Epilepsia 2018

Formalation 1: Nanostructured Lipid Carriers (NLCs)

Combined with specific chemical requirements, the nano-size introduces enhanced functional properties - such as improved solubility, stronger interaction with mucosa, better permeation, surface functionalization, etc. - which ultimately have positive influence on drug targeting, absorption, biodistribution, release (pharmacokinetic)

Spontaneously self-assembled system composed of a mixture of solid and liquid lipids



Ensure encapsulation of hydrophobic compounds

Superior characteristics compared to other nanocarriers:
- ✓ Targeted delivery
- ✓ Biocompatible
- ✓ Biodegradable
- ✓ Capacity to penetrate biological membranes
- ✓ Controlled drug release
- ✓ Drug protection
- ✓ Enhanced stability
- ✓ Surface versatility

Coupled with other strategies for prolonged delivery and higher bioavailability: surfactants for drug permeation and mucoadhesives for longer residence time

Available studies on drug loaded NLCs to treat central nervous system disease with high brain deposition

Khan S et al. An Overview of Nanostructured Lipid Carriers and its Application in Drug Delivery through Different Routes. Adv Pharm Bull 2023, 13, 3, 446-460.
Formica ML et al. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. Applied Materials Today 2022, 29, 101631.
Viegas C et al. Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers: A Comparative Review. Pharmaceutics 2023, 15, 1593.
Khan N et al. Nanostructured lipid carriers-mediated brain delivery of carbamazepine for improved in vivo anticonvulsant and anxiolytic activity. Int J Pharm 2020, 15, 577, 119033.

Formulation 1: Preparation of Blank and Drug Loaded NLCs and Characterization

Optimized NLCs preparation conditions (Lipid A: Lipid B - 80:20 ratio, lipid mixture and Tween 80 concentration)

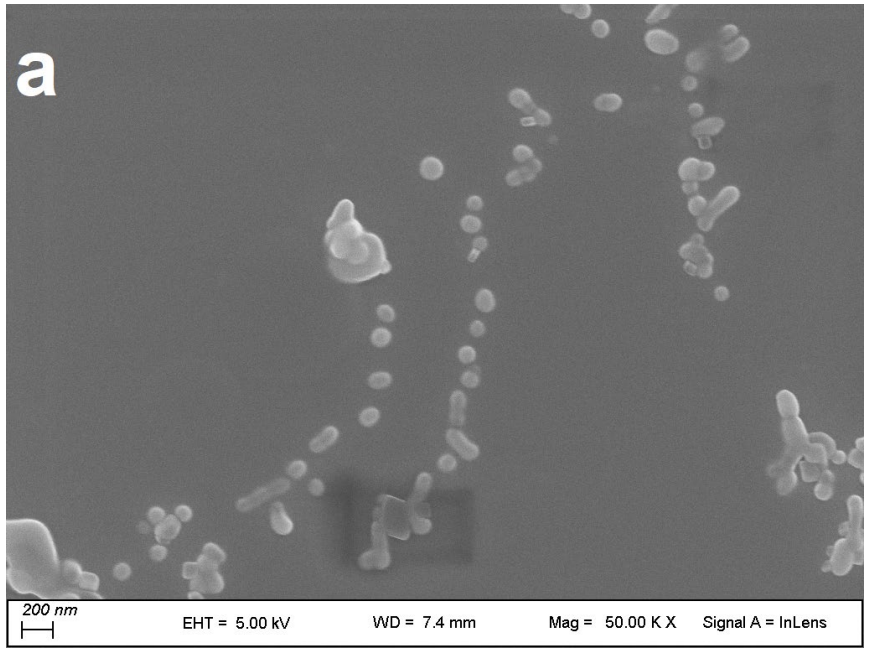
	Mean diameter (nm)	Polydispesidty index (PDI)	Zpotential (mV)
Blank NLCs	89.2 ± 4.1	0.2 ± 0.02	- 4.4 ± 1.5
NLCs (1% w/w drug)	87.9 ± 7.2	0.2 ± 0.02	- 2.9 ± 0.9

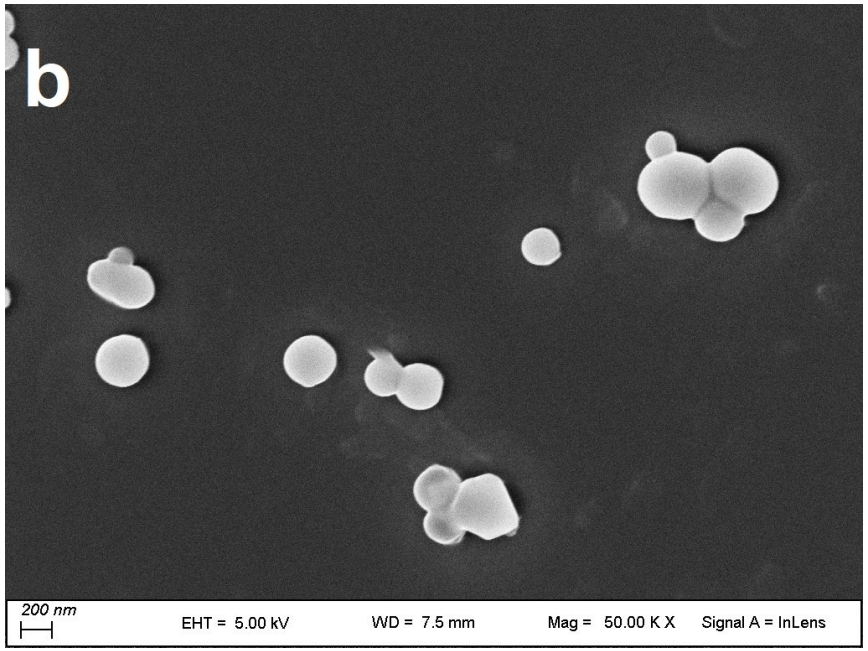
EE: 82.8 ± 3.6 %
DC: 0.82 ± 0.04%

Monodisperse NLCs population with suitable size

Target size range for N2B formulation: 50 - 200 nm

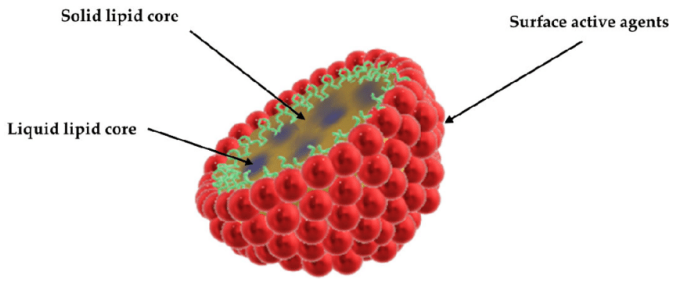
Spherical morphology of NLCs

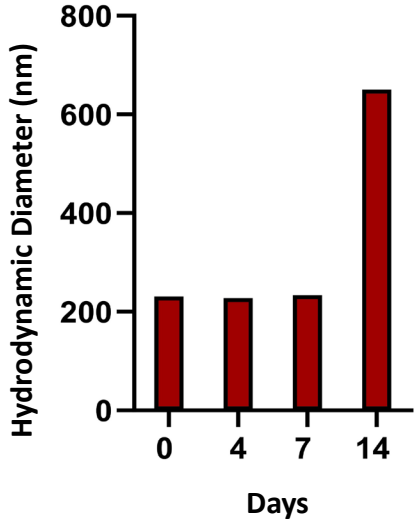


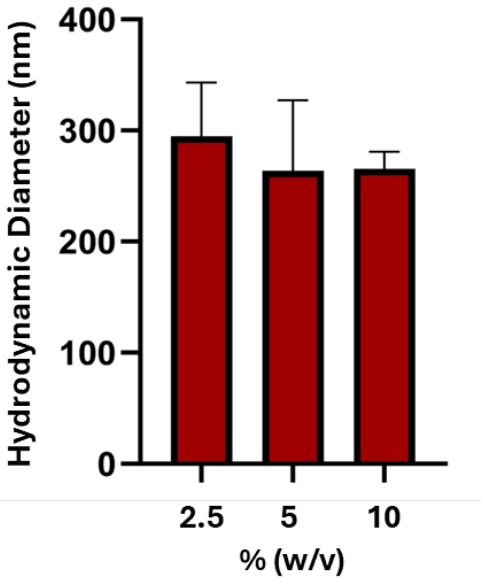


Bonaccorso A et al. Int J Nanomedicine 2024, 19, 5619–5636.

Formulation 1 : Addition of a Surface-Active Agent

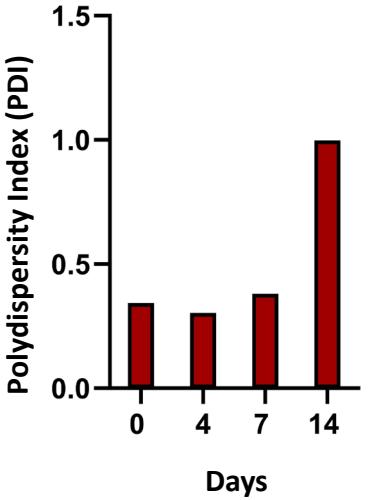




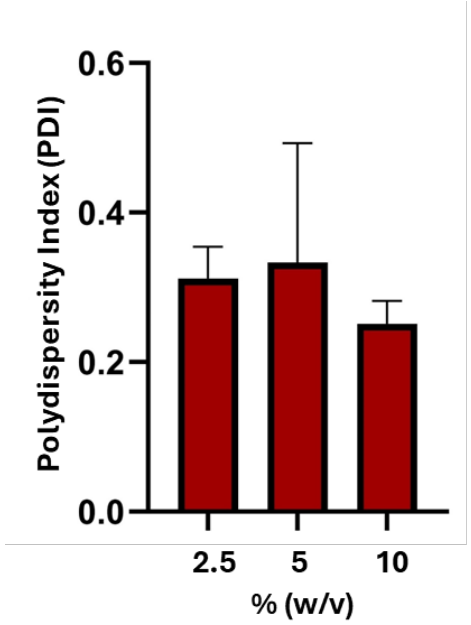


Lyophilization

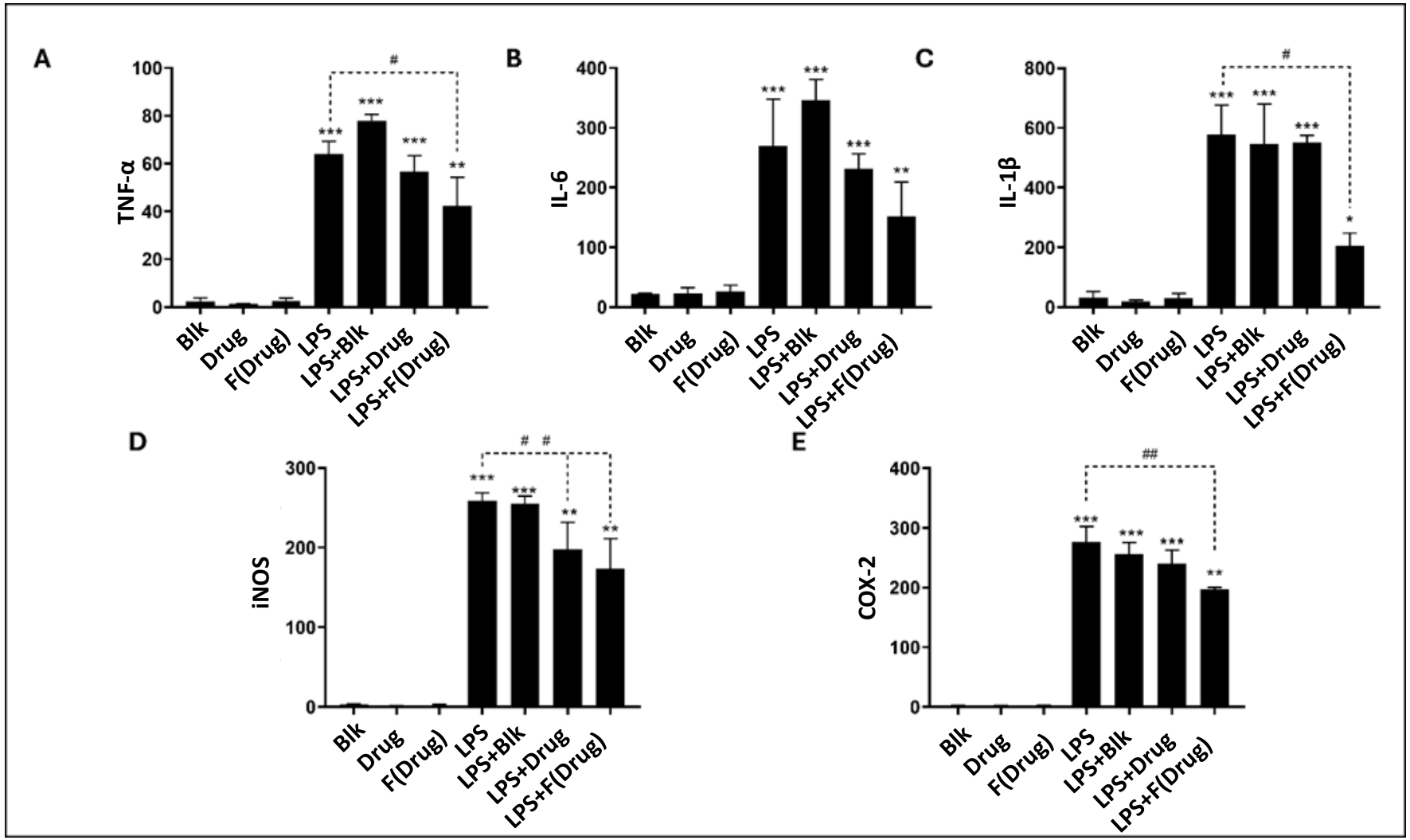
- Sucrose
- Trehalose
- L-Glycine

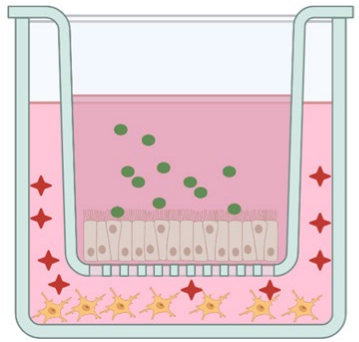


At 4°C



Formulation 1 : In Vitro Efficacy Test





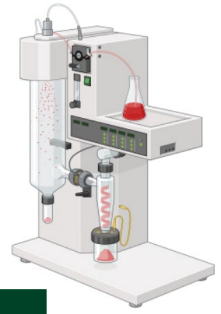
nasal ephitelium (RPMI2650 cells)

Microglia (HMC3 cells)

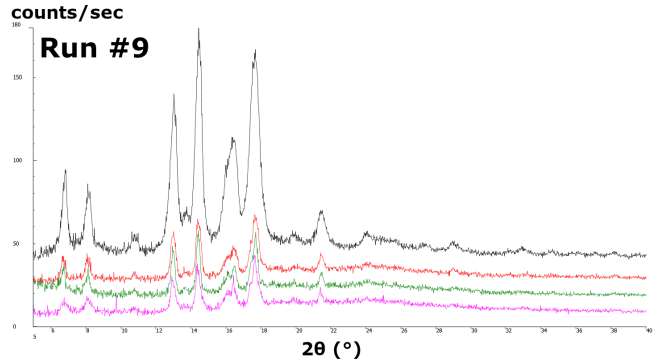
LPS

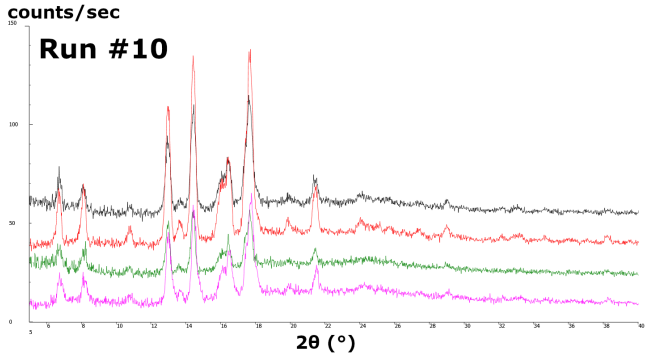
Formulation

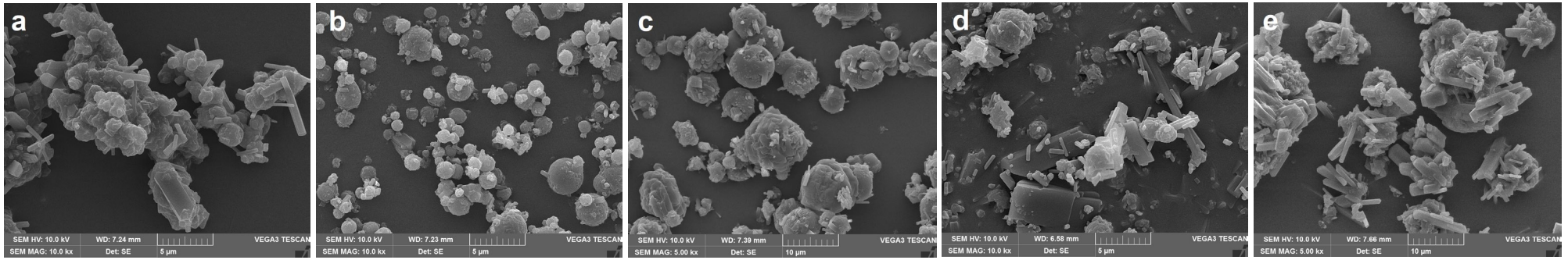
Formulation 2: Spray Dried Powder



Run	Inlet temperature (°C)	Outlet temperature (°C)	Feed rate (mL/min)	Nozzle diameter (mm)	Gas flow rate (L/h)	Yield (%)
1	78	49	1.5	140	473	10
2	85	38	1.5	140	473	14
3	85	43	3.0	140	473	5
4	85	53	0.9	140	473	15
5	85	56	0.3	140	473	3
6	90	52	1.5	140	473	41
7	95	58	1.5	140	473	39
8	95	44	3.6	140	473	22
9	95	52	4.5	140	473	48
10	95	62	4.5	150	246	28

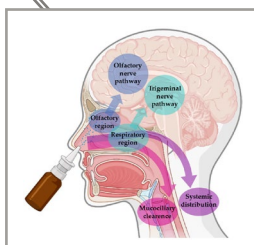




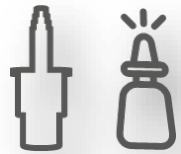


Take Away Messages

Harro Höfliger
ALL YOU NEED



Nasal Drug Delivery has been growing more and more through the recent years, and it is generally expected to grow even more



Liquid formulations are still the first go to option, but nasal powders are on the horizon

505b(2) shorten application process is very attractive for companies to explore nasal drug delivery as alternative pathway or as part of drug life cycle management

Nasal delivery is particularly advantageous for the repurposing of molecules for various applications (from vaccination to nose-to-brain delivery to rescue medications)

Acknowledgments

INTO accelerating inhalation development

Harro Höfliger ALL YOU NEED

Harro Höfliger
Marco Laackmann
Karin Marek

Aptar Pharma
Reenal Gandhi

DFE Pharma
Maribel Bogalo
Ross Blezard
Xander van Leeuwen

Sterling
Andrea Silvestri
Anna Vivani
Stefania Kern

Harro Höfliger

ALL YOU NEED

Irene Rossi, PhD

Respiratory Science Expert

Helmholtzstraße 4
71573 Allmersbach im Tal
Germany

+49 7191 501-4122

Irene.Rossi@hoefliger.de