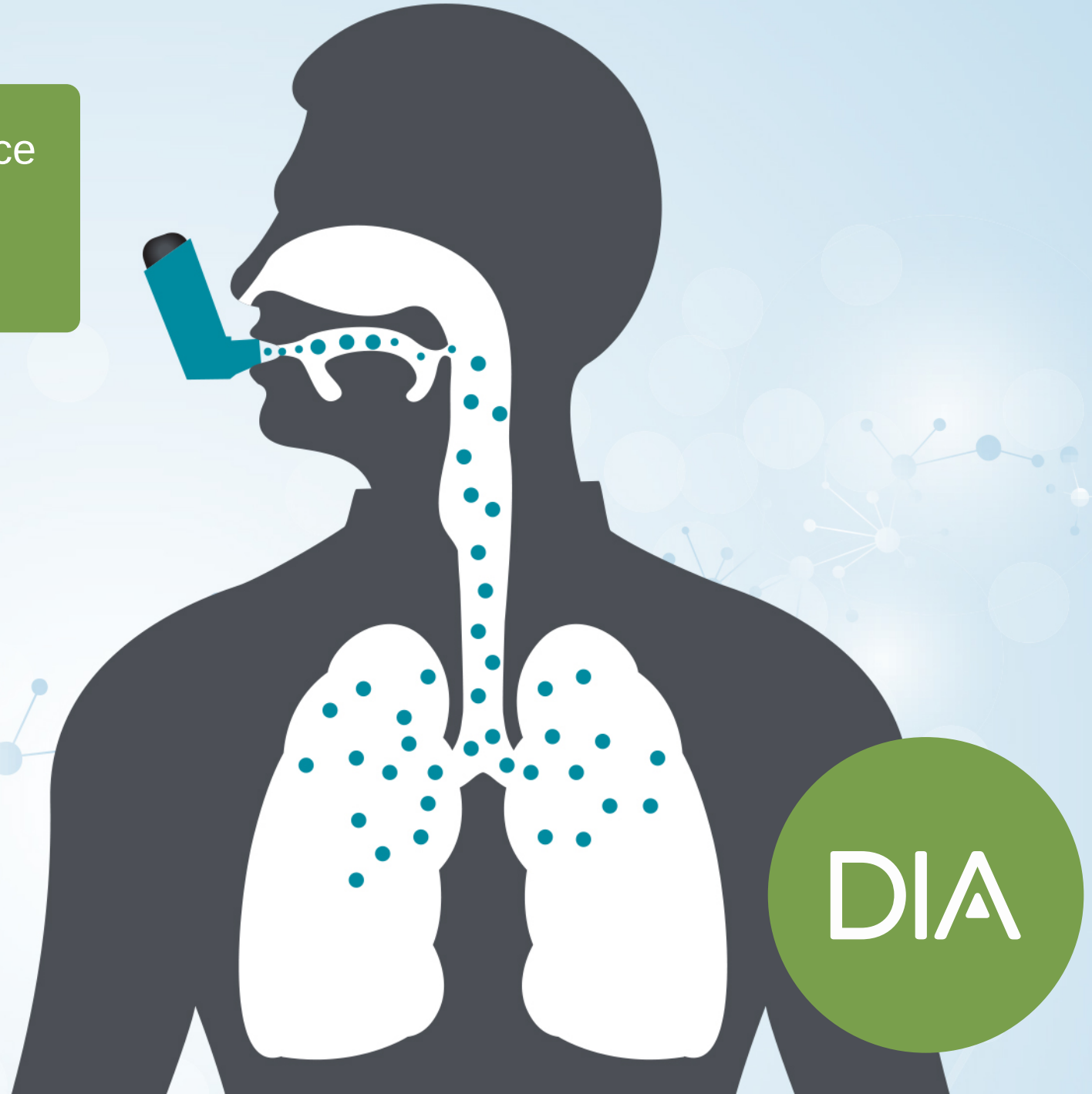
DIA/FDA Complex Generic Drug-Device Combination Products Conference

October 19-20 | Virtual



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Pharmacokinetic Comparison of Locally Acting Nasal Suspension Spray Products

- **Speakers**: Günther Hochhaus and Jürgen Bulitta

- **UF:** S Berger, E Amini, MJ Chen, A Kurumaddali, U Schilling, Y Jiao, S Drescher, J Thomas, SM Baumstein, A. Wlodarski, L Winner, JB Bulitta, G Hochhaus
- **FDA**: DS Conti, O Oguntimein, R Delvadia, B Saluja, L Lee
- **U Bath:** J Shur, R Price, T Iley (Intertek)
- **VCU:** M Hindle , X Wei
- **Worldwide Clinical Trials**: C Carrasco
- **Funding**: HHSF223201310220C

Regulatory Landscape for BE Assessment of Locally Acting Nasal Sprays

- Solution based Nasal Sprays: *In vitro* alone is sufficient
- Suspension based Nasal Sprays:
  - Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation.
  - *In vivo* studies (PK and clinical Endpoint Studies) are recommended due to an **inability**, at the present time, **to adequately characterize drug particle size distribution (PSD) in aerosols and sprays**

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action Nasal BE Guidance (2003)

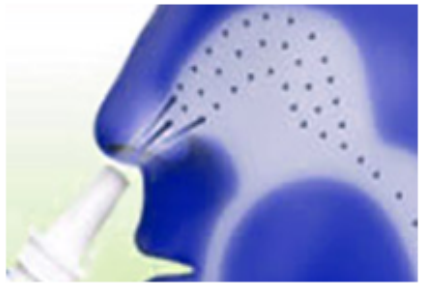
Guidance : BE of Mometasone Furoate Nasal Spray (Suspension)

- Single Actuation Content
- Droplet Size Distribution by Laser Diffraction
- Drug in small Particles/Droplets
- Spray Pattern / Plume Geometry
- Priming / Repriming
- PK-Bioequivalence Study → standardized dosing procedure!

- Clinical Endpoint BE Study (Multi-Center Study)
  - Reason: In vivo studies are necessary as particle size cannot be easily determined in formulation

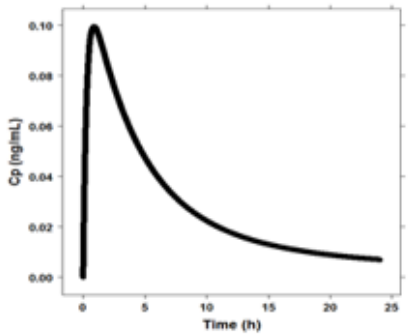
Fate of Intranasal Corticosteroids

Deposition in nasal cavity and pharynx



Therapeutic effects

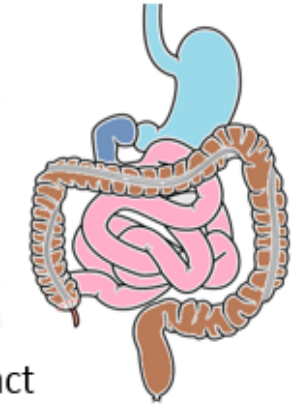
Absorption from the nasal tissue



Systemic circulation

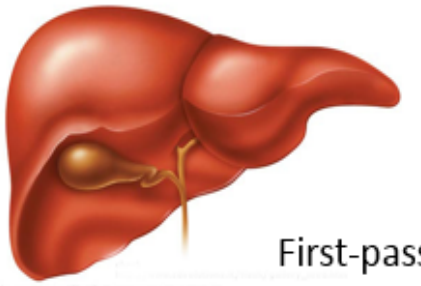
Systemic side effects

Swallowed + CL_{muc}



GI-tract

Absorption from gut



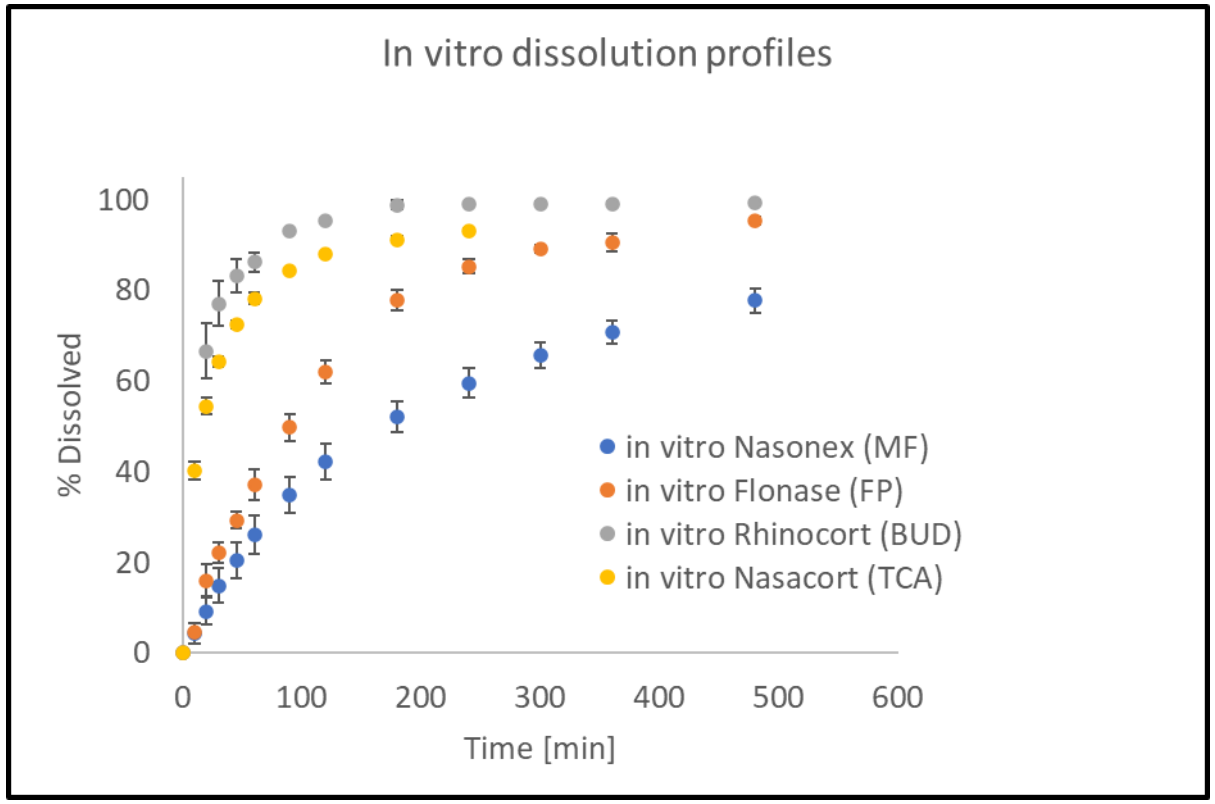
Liver

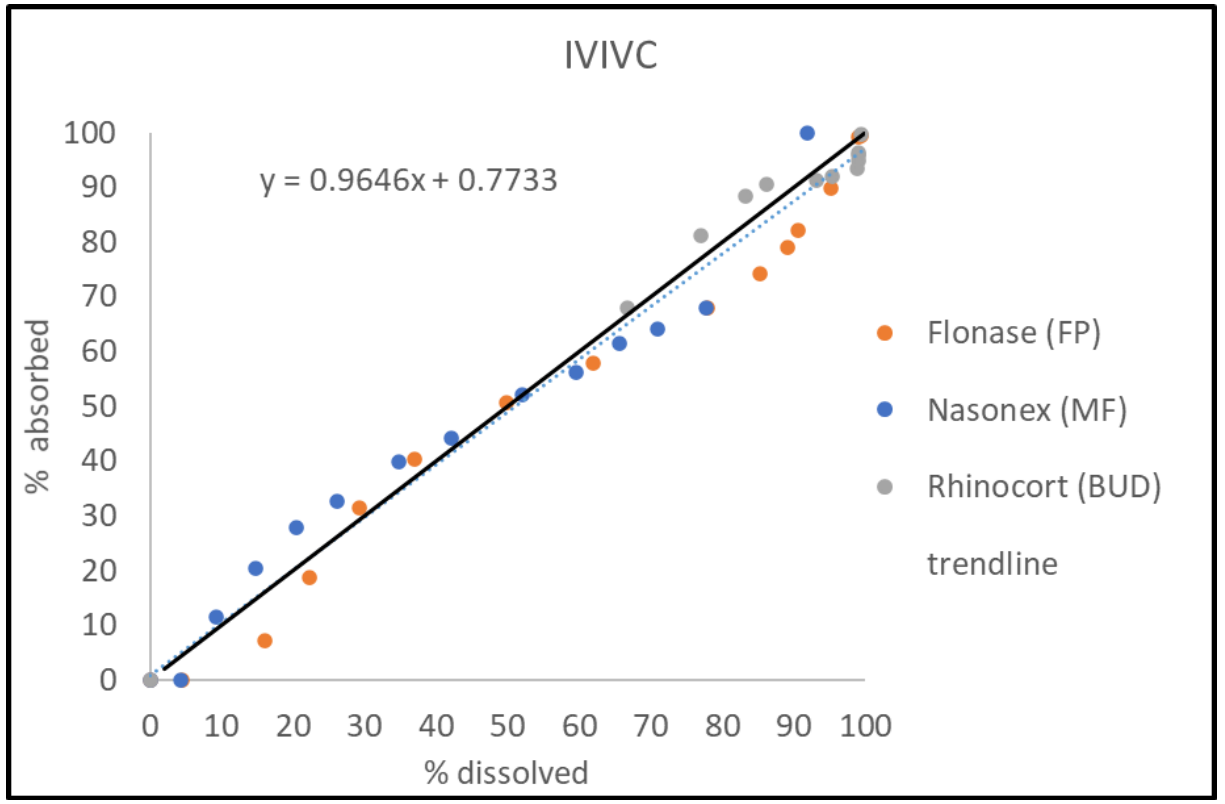
Oral Bioavailability

First-pass inactivation

How can we evaluate Equivalence in Particle Size within the Formulation

- **MDRS**: Morphologically Directed Raman Spectroscopy
- Dissolution Tests → Pharmacokinetics





Possible Alternative Regulatory Pathways for Suspension Nasal Sprays:

- ***In Vitro Studies*** Including PSD (MDRS), and Dissolution Test + **Pharmacokinetics**

- **In Vitro Alone**: Including Particle Size (MDRS), Dissolution Test

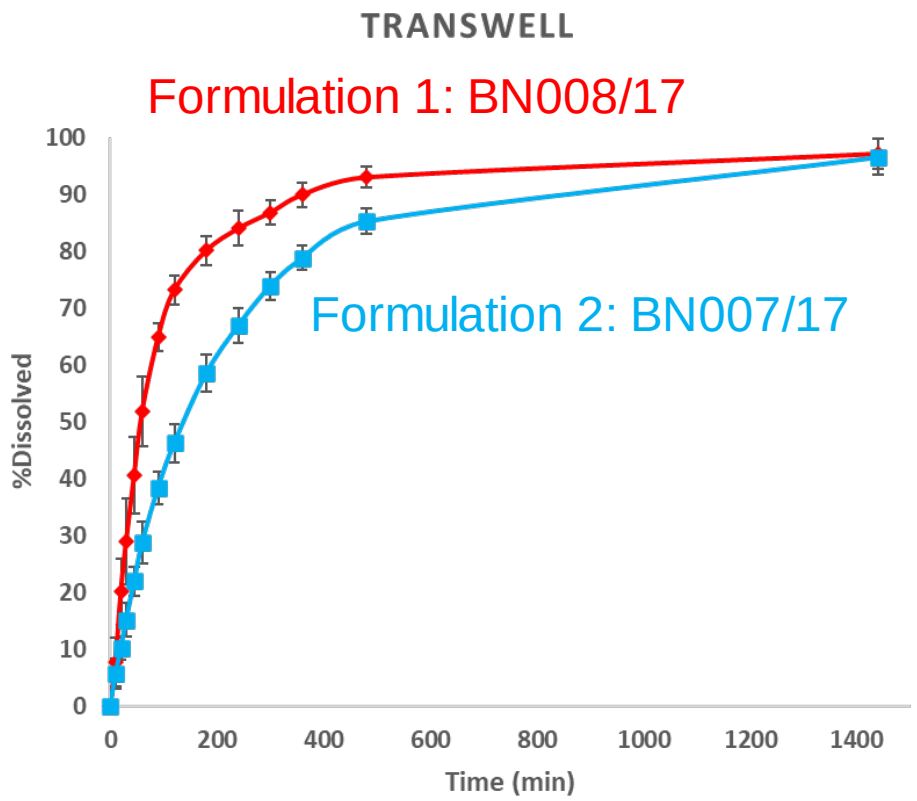
Study Design

- Prepare Mometasone Furoate Formulations that Differ in Particle Size Distribution
- Perform detailed *in vitro* characterization (via MDRS), Dissolution test + Standard Evaluation
- Perform human Pharmacokinetic Study

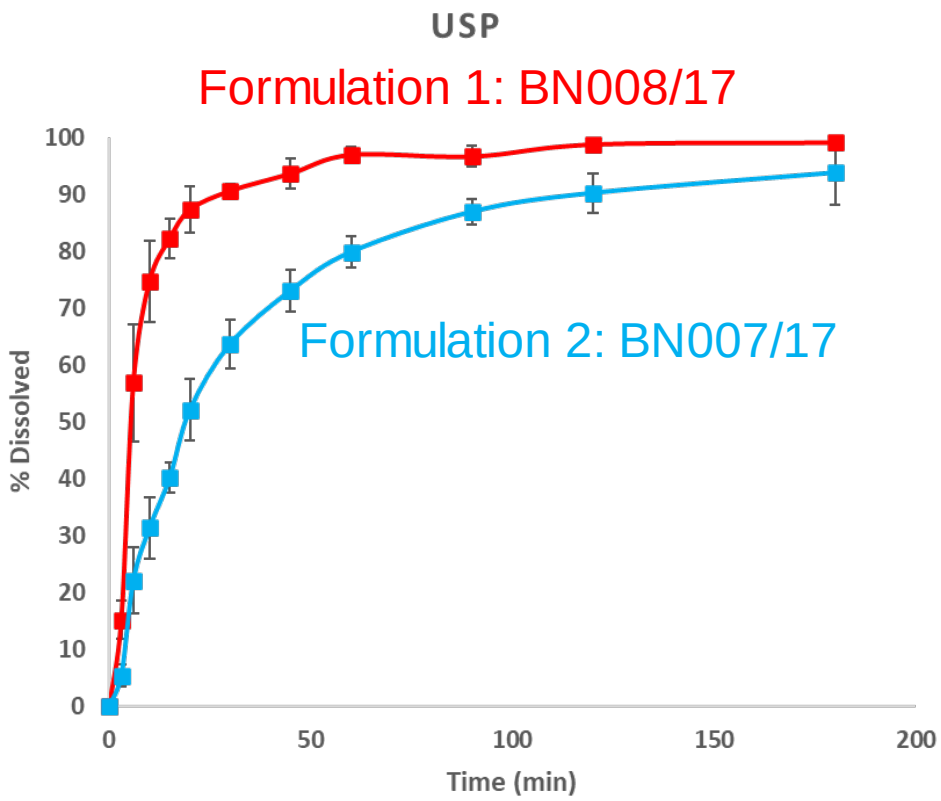
- Particle Size:
  - Batch Material from Sterling: about 1.3 µm vs 3 µm
  - In-formulation (MDRS): Dv(50): Batch 008: **3.17 µm** vs Batch 007: **5.5 µm**

- Delivered Dose (at 14 months):
  - Batch 1: **43.7 µg** vs. Batch 2: **44.6 µg**

Dissolution of MF Nasal Spray Formulations



Formulations	Difference Factor (f1)	Similarity Factor (f2)	Results
I vs. II	23.44	37.73	Non-Equevalent

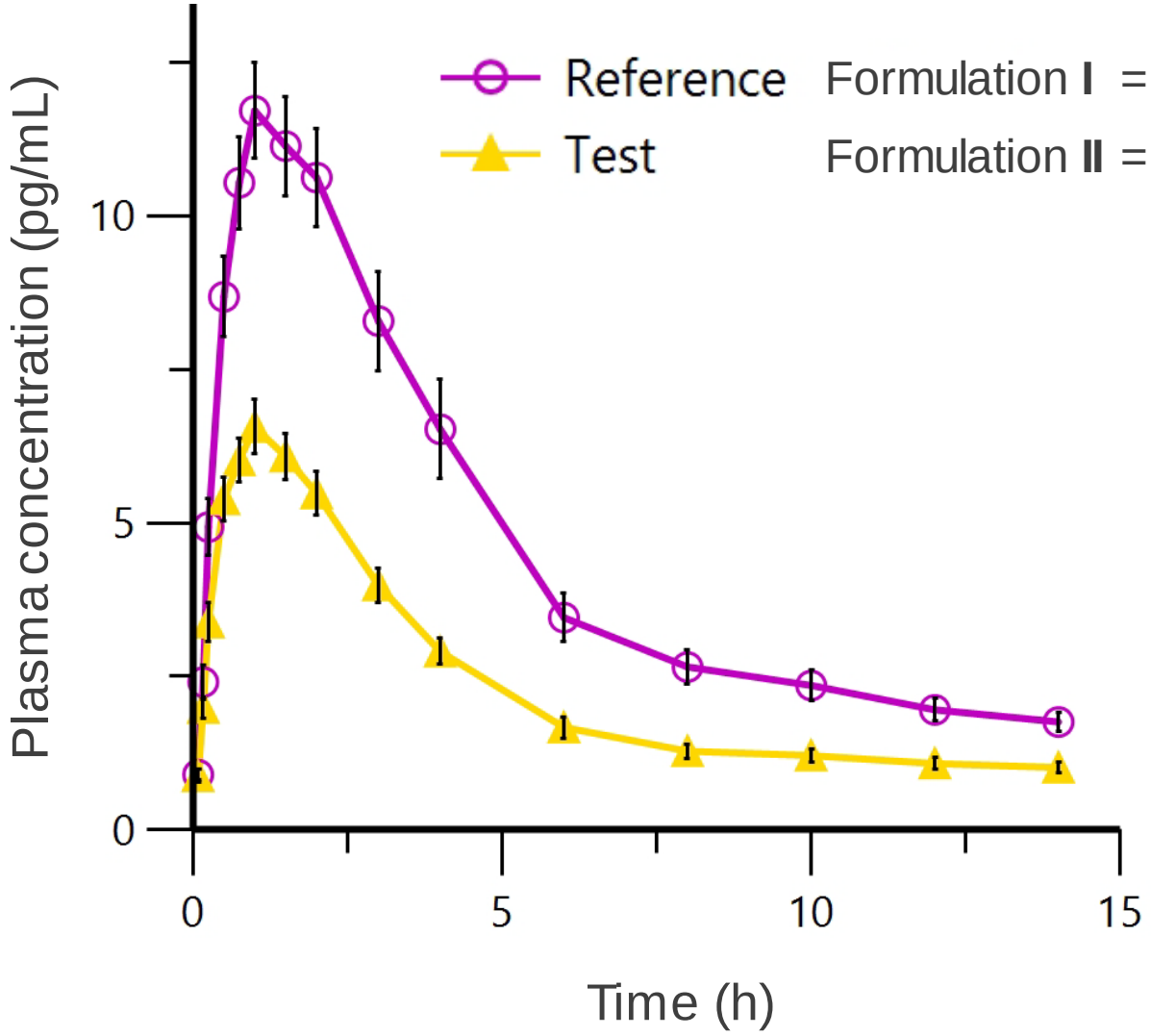


Formulations	Difference Factor (f1)	Similarity Factor (f2)	Results
I vs. II	28.41	29.60	Non-Equevalent

PK Study Design

- 2-way, Cross-over, Double blind
- Carefully standardized Dosing (administered by experienced clinical personnel)
- 44 healthy volunteers with data on both formulations
- Dose: 2 Actuations (‘sprays’) into each nostril, i.e. 4 actuations total, → 200 µg dose
- Non-compartmental PK Analysis (AUC_{0-t}, C_{max})
- Bioequivalence (BE) statistics analysis

Mean Plasma Conc-Time Profiles (Reference vs Test)



Parameter	Formulation	Mean	SD
Cmax	I (small)	13.6	6.1
(pg/mL)	II (large)	7.3	2.9
AUClast	I (small)	63.4	36.0
(pg/mL·h)	II (large)	32.1	15.5
Tmax	I (small)	1.29	0.74
(h)	II (large)	1.09	0.52
T1/2	I (small)	9.75	3.7
(h)	II (large)	10.2	3.5
Dv(50)	I (small)	3.2	(4.3%)
(µm)	II (large)	5.5	(15.8%)

Bioequivalence Summary

	Point estimate (%)	Lower bound of 90% CI (%)	Upper bound of 90% CI (%)	Conclusion	ANOVA-CV
AUC_{last}	53.6	47.6	60.0	Not bio-equivalent	33%
C_{max}	55.3	49.0	62.5	Not bio-equivalent	36%

Conclusion for Pharmacokinetics

- Formulation with larger Particle size shows **smaller AUC and smaller Cmax**
- **Slower Dissolution** results in **more particles** being **removed by ciliary clearance**
- **PK** is sensitive to detect differences in Particle Size Differences
- Dissolution studies show similar sensitivity to detect Differences

Overall Conclusion for Suspension Based Nasal Sprays

- Clinical Studies are NOT necessary, since PK can detect differences in Particle Size:

  In vitro, incl. MDRS, dissolution test + PK

- Alternatively: *In vitro* Assessment of Suspension based Nasal Sprays, alone, seems possible, if alternative *in vitro* tests are being performed and included:

  In vitro studies including MDRS + Dissolution Tests.