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Dissolv*It*® – evaluation report and presentation of data

from the FDA funded study on Inhalation Sciences *in vitro* module

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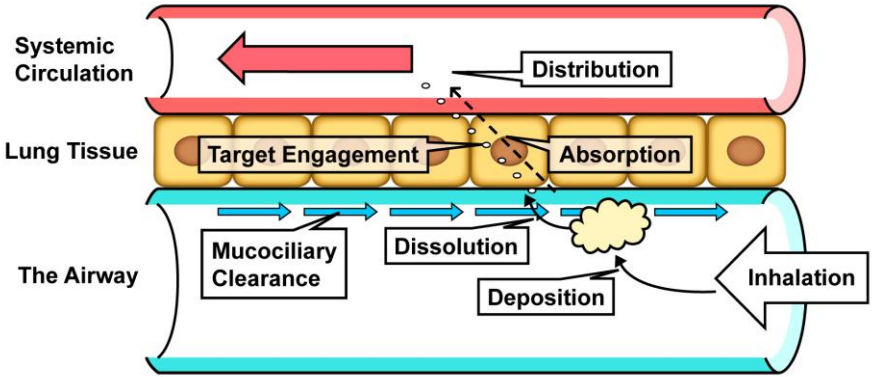
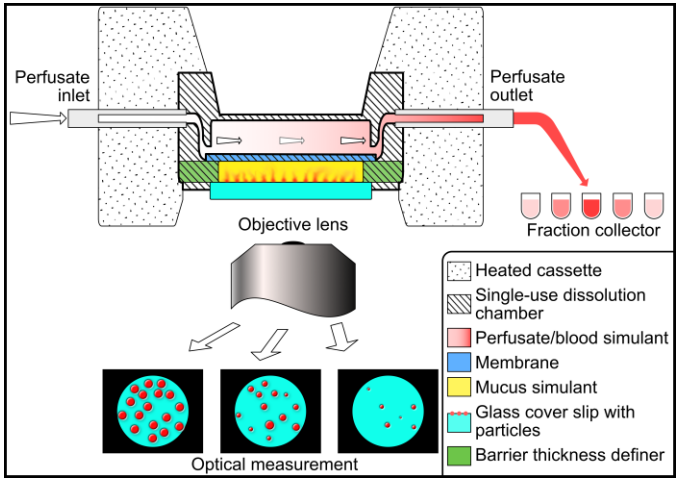
Introduction

- The Dissolv*It*® system is an *in vitro* test model/dissolution apparatus that is built to resemble relevant lung physiology for evaluation of the dissolution- and absorption of inhalable drugs.

- Drug particles are evenly distributed over glass cover slips and dissolved into a mucus simulant and then absorbed into flowing perfusate, thereby creating *in vivo* like conditions and generating time-concentration curves with T_{max} and C_{max} as measurable parameters.





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Project aims

- The aims of the FDA funded project were to:
  - **Aim 1**: Evaluate the discriminatory ability of the Dissolv*It* system using different formulations with known **differences or similarities**.
  - **Aim 2**: Directly compare Dissolv*It* data to IPL data in rat *ex vivo* as well as to clinical data *in vivo*.
  - **Aim 3**: Investigate the potential for *in vivo* predictability of Dissolv*It* data by performing physiologically-based biopharmaceutical modeling (PBBM) .

Inhalation products tested in Dissolv*it* within this project

16 test products

6 manufactured micronized dry powders (pure API)

9 commercially available DPIs

1 commercial available pMDI

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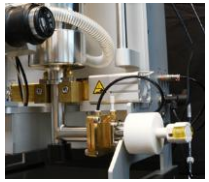
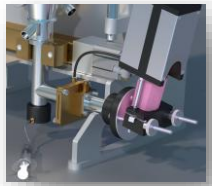
Methods: Aerosolization and dose deposition (PreciseInhale®) dissolution testing (Dissolv*lt*®)

6 manufactured micronized dry powders (pure API)

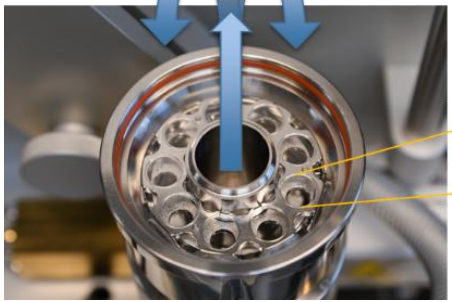
9 commercially available DPIs

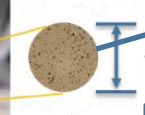


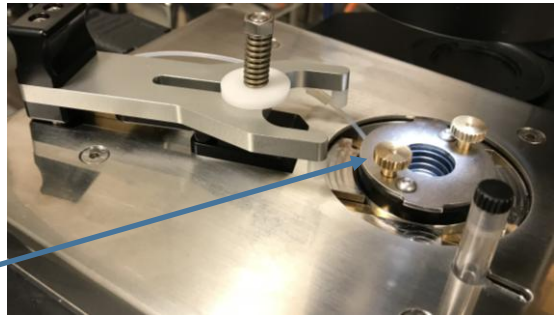
1 commercial available pMDI



Test product







Dissolution testing in Dissolv*lt*

Aerosolization and dose deposition onto glass cover slips with PreciseInhale

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Aim 1: Evaluate the discriminatory ability of the DissolvIt system using different formulations with known differences or similarities

ISAB code	Test product	Evaluations performed
IS194	Budesonide, DISCUS, 3.29 µm (X50)	Data evaluation of APSD and dissolution of products where the API PSD and API manufacturing method are varied.
IS195	Budesonide, DISCUS, 2.14 µm (X50)	
IS196	Budesonide, UMAX, 1.54 µm (X50)	

ISAB code	Test product	MMAD (µm)	GSD
IS194	Budesonide, DISCUS, 3.29 µm (X50)	2.34 ± 0.00	2.33 ± 0.11
IS195	Budesonide, DISCUS, 2.14 µm (X50)	1.78 ± 0.18	2.14 ± 0.05

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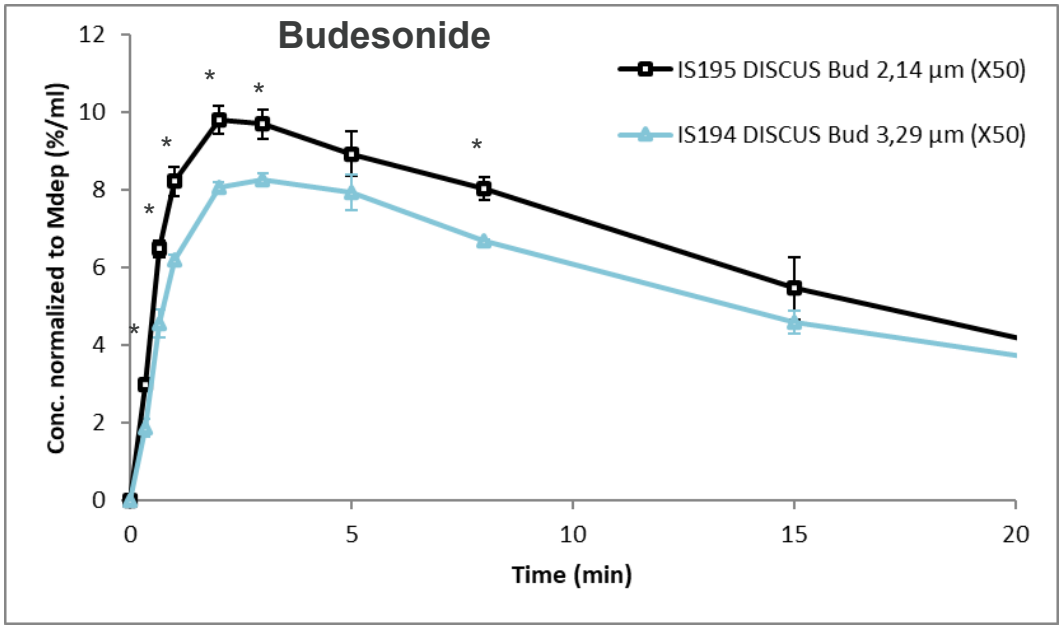
Aim 1: Budesonide – different sizes, differences expected to be seen



*Statistically significant difference p<0.05, Student's t-test, two-sided, assuming similar variance

The smaller particles (IS195) are dissolved faster, that is demonstrated by identifying a shorter T_{max}, higher normalized C_{max} …..

Dissolv*it* detects differences

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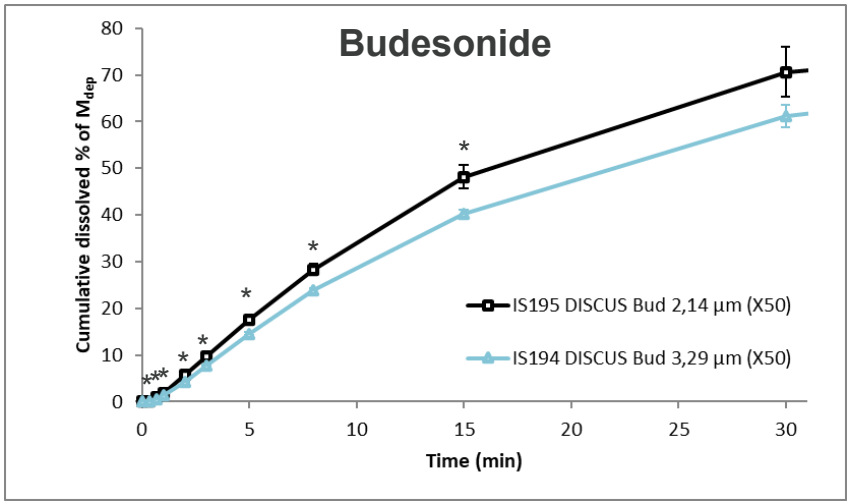
Aim 1: Budesonide – different sizes, differences expected to be seen



*Statistically significant difference p<0.05, Student's t-test, two-sided, assuming similar variance

….and higher values of the cumulative dissolution.

Dissolv*it* detects differences

ISAB code	Test product	Normalized C_{max} (%/mL)	T_{max} (min)	Cumulative dissolution at 15 min
IS194	Budesonide, DISCUS, 3.29 µm (X50)	8.3 ± 0.2	3.0 ± 0.0	40.4 ± 0.7
IS195	Budesonide, DISCUS, 2.14 µm (X50)	9.8* ± 0.4	2.0* ± 0.0	48.1* ± 2.5

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Aim 1: Evaluate the discriminatory ability of the DissolvIt system using different formulations with known differences or similarities

ISAB code	Test product	Evaluations performed
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IS195	Budesonide, DISCUS, 2.14 µm (X50)	
IS196	Budesonide, UMAX, 1.54 µm (X50)	

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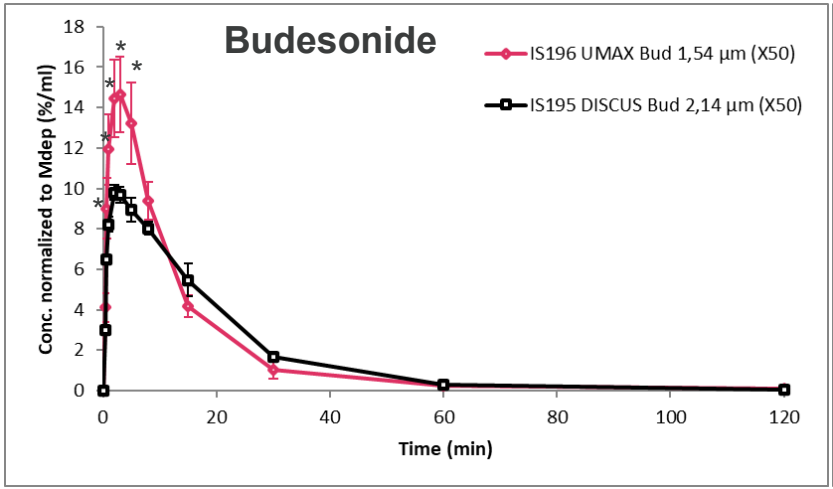
Aim 1: Budesonide – different manufacturing methods

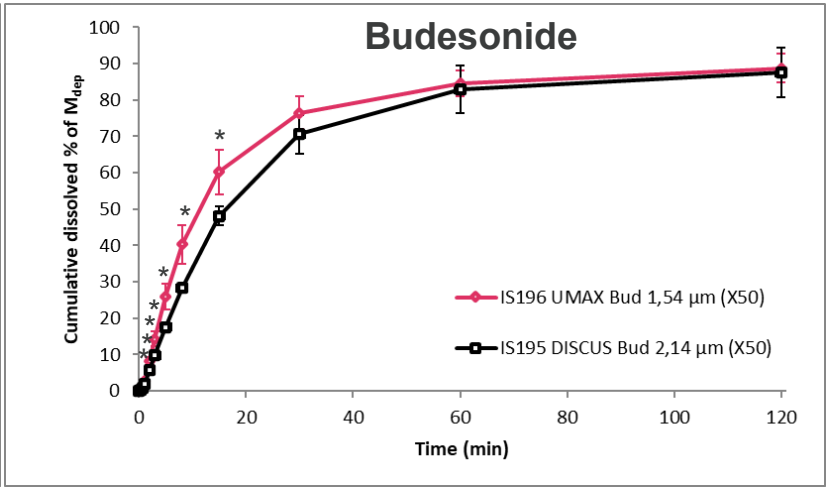
ISAB code	Test product	Manufacturing method	MMAD (µm)	GSD
IS195	Budesonide, 2.14 µm (X50)	DISCUS	1.78 ± 0.18	2.14 ± 0.05
IS196	Budesonide, 1.54 µm (X50)	UMAX	1.59 ± 0.12	1.98 ± 0.13

- DISCUS = Dispersive crystallization with ultrasound, gives more ”normal” crystalline particles
- UMAX = ultrasound mediated amorphous to crystalline transition, gives crystalline particles with round morphology, more rugosity

Aim 1: Budesonide – different manufacturing methods,

differences expected to be seen





*Statistically significant difference p<0.05, Student's t-test, two-sided, assuming similar variance

ISAB code	Normalized C_{max} (%/mL)	Cumulative dissolution and absorption (%) after								
		20 s	40 s	1 min	2 min	3 min	5 min	8 min	15 min	30 min
IS196, Bud UMAX 1.54 µm (X50)	14.6 ± 1.9*	0.3±0.1	1.2±0.2*	2.7±0.4*	8.2±1.2*	14.3±2.0*	26.0±3.5*	40.4±5.3*	60.2±6.1*	76.4±4.5
IS195, Bud DISCUS 2.14 µm (X50)	9.8 ± 0.4	0.2±0.0	0.9±0.0	1.9±0.0	5.7±0.2	9.8±0.3	17.6±0.7	28.3±1.2	48.1±2.5	70.6±5.3

Dissolv*it* detects differences

The more rough UMAX particles were expected to dissolve faster.

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Aim 1: Evaluate the discriminatory ability of the DissolvIt system using different formulations with known differences or similarities

ISAB code	Test product	Evaluations performed
IS406	Symbicort Turbohaler 320/9 (Bud/For F), DPI	APSD determination and dissolution testing in DissolvIt for both APIs in a brand name product versus a generic product.
IS407	Bufomix Easyhaler (320/9) (Bud/For F), DPI	
IS408	Seretide Evohaler FP/SX (250/25), pMDI	APSD determination of both APIs in an *in vitro* and an *ex vivo* set-up. Dissolution testing of both APIs in Dissolv*It* and generation of lung absorption data in IPL (*ex vivo*) for both APIs. Comparison of the generated *in vitro* and *ex vivo* data with existing *in vivo* data. PBB modeling of the Dissolv*It* generated FP data.

Test product	MMAD of Bud (µM) (n=3)	GSD of Bud (n=3)	MMAD of For (µM) (n=3)	GSD of For (n=3)
Symbicort Turbohaler, IS406	3.11 ± 0.17	1.77 ± 0.01	3.12 ± 0.19	1.76 ± 0.01
Bufomix Easyhaler, IS407	3.31 ± 0.15	1.77 ± 0.00	3.79 ± 0.22	1.63 ± 0.00

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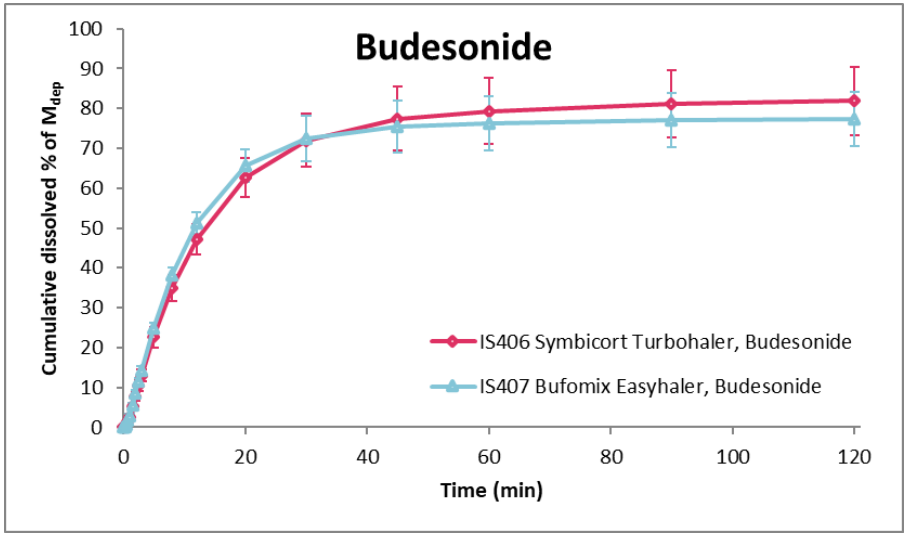
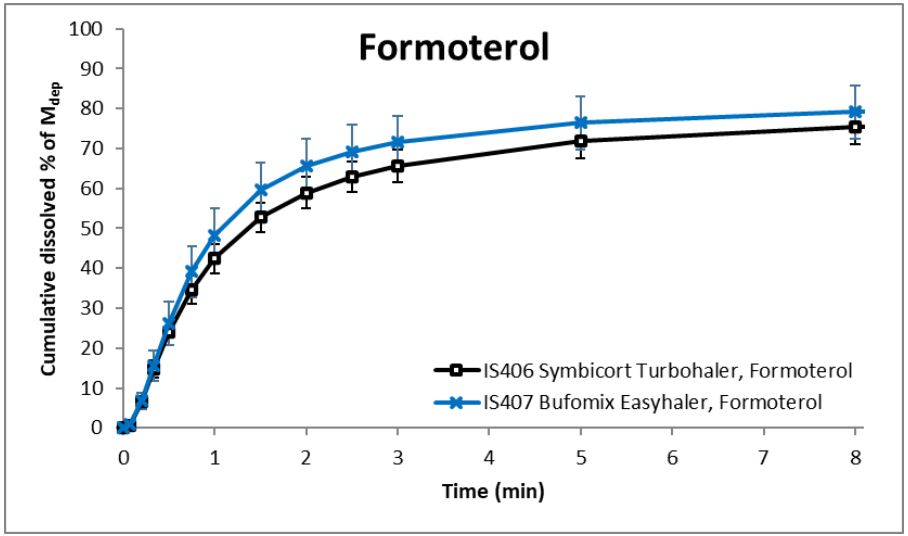
Brand name (Symbicort Turbohaler) and generic product (Bufomix Easyhaler) – similarities expected to be seen#

Symbicort Turbohaler is a brand name product in Europe, and Bufomix Easyhaler is now an approved generic product in Europe. Both contains two APIs, budesonide and formoterol.





No statistically significant differences (Student's t-test, two-sided assuming similar variance).

Dissolv*It* confirms similarities seen in clinical data#.

#Reference including studies performed in order to get Bufomix Easyhaler approved as a generic to Symbicort Turbohaler.: Lähelmä, S., et al., *Equivalent Lung Dose and Systemic Exposure of Budesonide/Formoterol Combination via Easyhaler and Turbuhaler.* J Aerosol Med Pulm Drug Deliv, 2015. **28**(6): p. 462-73.

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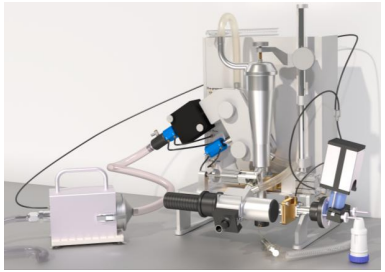
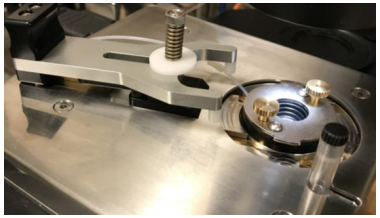
Aim 2: Directly compare Dissolv*It* data to IPL data in rat *ex vivo* as well as to clinical data *in vivo*

PreciseInhale



Dissolv*It* – *in vitro*



- Non-biological system physiologically resembling the lung
- Comprises an artificial air-blood barrier with a mucus simulant
- System perfused with a blood simulant; dissolved and absorbed API detected in the single-pass perfusate over time (4 h)

Isolated and Perfused Lung (IPL) – *ex vivo*

- Specific exposure of the rat lung
- Lung ventilated and perfused during the experiment (2 h)
- Perfusate analysis provides lung specific PK-data
- Substance remaining in lung completes a mass balance

Clinical exposures – *in vivo*

- Regional lung dosing with PreciseInhale
- Blood samples collected for 24 h
- API analysis in plasma samples
- Clinical study performed: Gerde, P., et al., *Regional lung targeting with a fluticasone/salmeterol aerosol using a bolus breath hold method of the PreciseInhale® system: A first evaluation in humans.* Eur J Pharm Sci, 2024. **196**: p. 106742.

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ISAB code	Test product	Evaluations performed
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System	Test Product	IS #	MMAD FP (µm) GSD FP	MMAD Sal (µm) GSD Sal
DissolvIt – *in vitro*	Seretide Evohaler (250/25), pMDI	408	**3.88 ± 0.10 1.71 ± 0.04**	**3.97 ± 0.10 1.69 ± 0.05**
IPL – *ex vivo*	Seretide Evohaler (250/25), pMDI	408	**3.98 ± 0.20 1.91 ± 0.08**	**4.07 ± 0.20 1.89± 0.08**
Clinical – *in vivo*	Seretide Evohaler (250/25), pMDI	n/a*	**4.22 ± 0.11 1.98 ± 0.02**	**4.55 ± 0.02 2.22 ±0.1**

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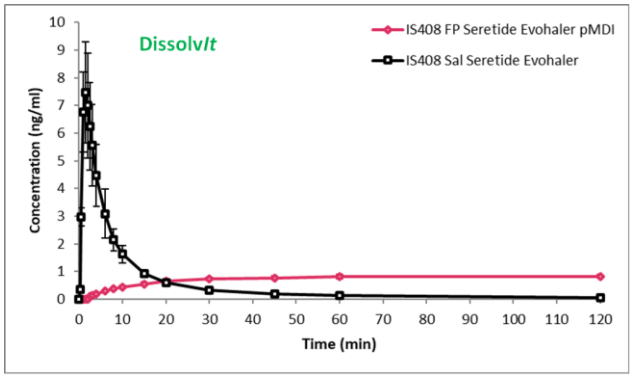
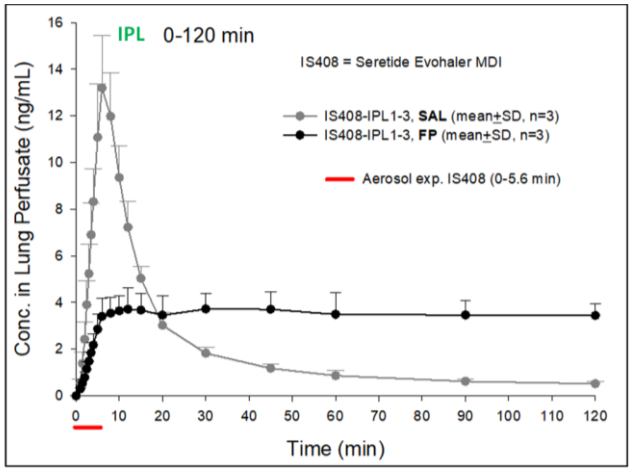
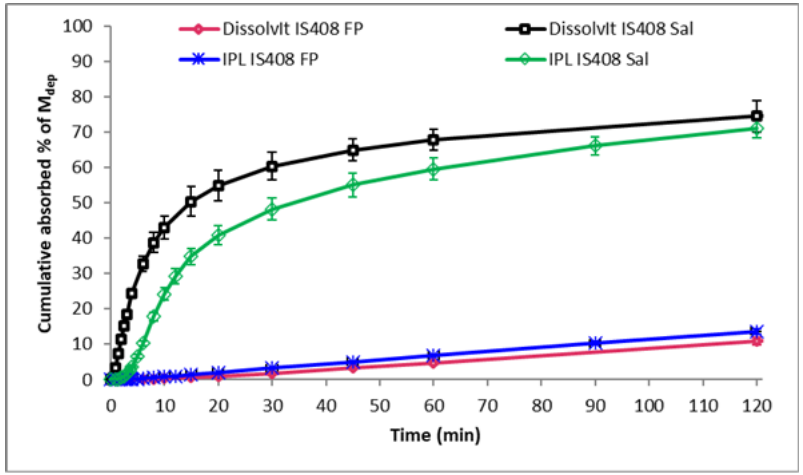
Dissolv*It* and IPL comparison – *in vitro ex vivo* correlation (IVEVC)







- Similar dissolution/absorption curves for both FP and Sal as well as same order of magnitude for C_{max} for both FP and Sal from Seretide Evohaler 250/25 in Dissolv*It* and IPL
- Similar dissolved and absorbed % API from Seretide Evohaler 250/25 in Dissolv*It* and IPL after 2 h for both FP (11% in Dissolv*It*, 14% in IPL) and Sal (75% in Dissolv*It*, 71% in IPL)
- The small differences seen can be explained by the system set-up/design such as time for dose deposition and lipid distribution in the air-blood barrier

Direct data comparison is possible between Dissolv*It* and IPL

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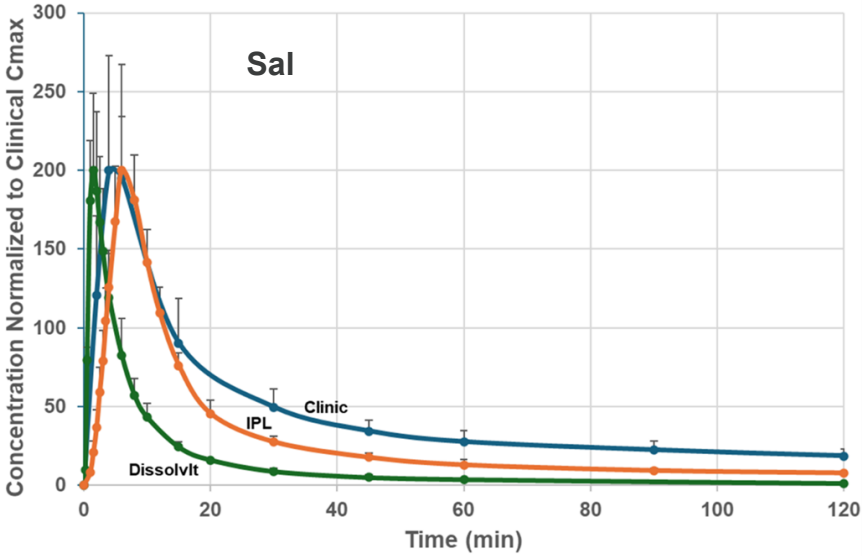
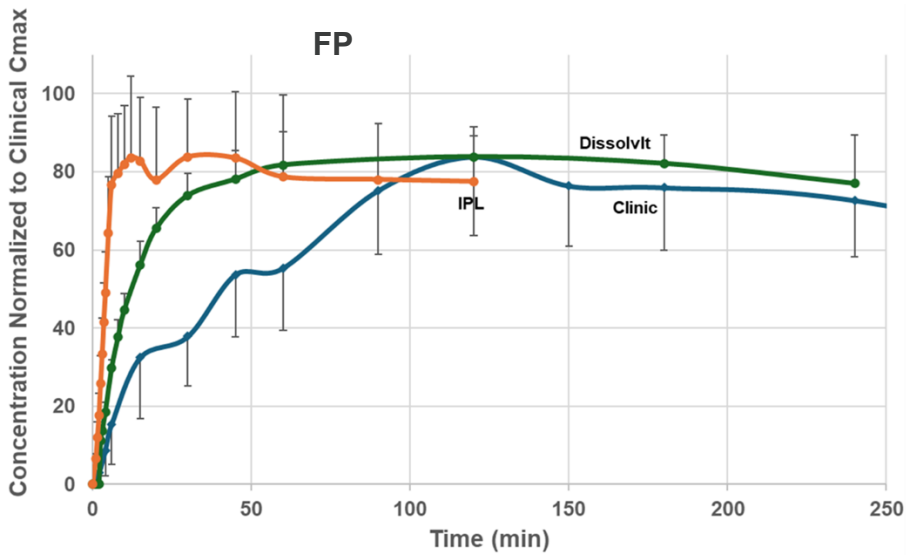
IVIVC – *in vitro/ex vivo in vivo* correlation





- Circulatory clearance of Sal and FP from Seretide Evohaler 250/25 pMDI in Dissolv*It* (green), IPL (orange) and clinic* (blue).

- Dissolv*It* data compares more directly to IPL data and describes dissolution and absorption of substance in the lung only whereas clinical data shows the additional effect of the substance passing into the blood circulation.

- Together with PBB modeling the Dissolv*It* FP data was used to predict a clinical profile.

*Gerde, P., et al., *Regional lung targeting with a fluticasone/salmeterol aerosol using a bolus breath hold method of the PreciseInhale® system: A first evaluation in humans.* Eur J Pharm Sci, 2024. **196**: p. 106742.

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Aim 3: Investigate the potential for *in vivo* predictability of Dissolv*It* data by performing physiologically-based biopharmaceutical modelling

- The FP dissolution data generated in Dissolv*It* for Seretide Evohaler 250/25 pMDI together with dose deposition data from literature were used for PBB modeling of a FP plasma concentration-time profile.

- This calculated profile was compared with the observed clinical data (Gerde, P., et al., *Regional lung targeting with a fluticasone/salmeterol aerosol using a bolus breath hold method of the PreciseInhale® system: A first evaluation in humans.* Eur J Pharm Sci, 2024. **196**: p. 106742.).

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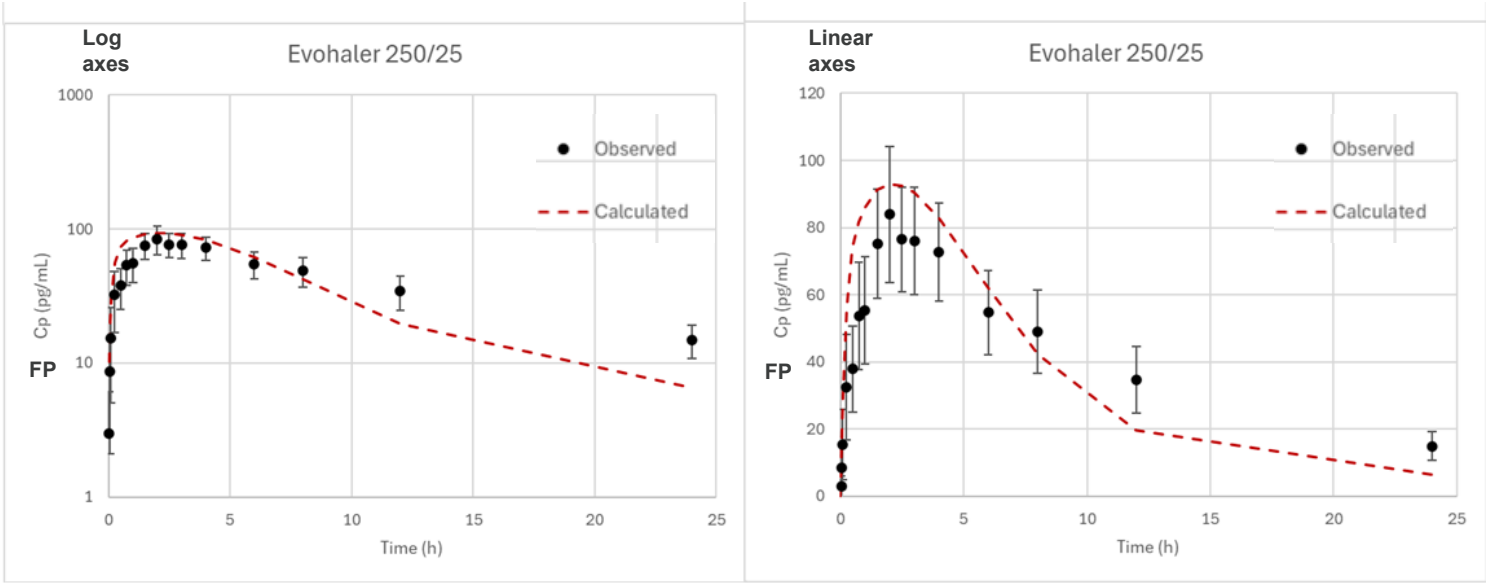
Can Dissolv*It* predict clinical data?

PBB modelling of FP in Seretide Evohaler 250/25 pMDI



PBB = physiologically-based biopharmaceutical, FP = fluticasone propionate, Cp = plasma concentration,
Red dotted line (calculated) = Dissolv*It* dissolution data after PBB modeling, Black dots (observed) = Observed clinical data

Dissolv*It* dissolution method predicted a clinically relevant dissolution rate for FP in Seretide Evohaler 250/25 pMDI

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Observed data: Gerde, P., et al., *Regional lung targeting with a fluticasone/salmeterol aerosol using a bolus breath hold method of the PreciseInhale® system: A first evaluation in humans.* Eur J Pharm Sci, 2024. **196**: p. 106742.

Conclusions

- Dissolv*It* detects expected differences in dissolution/absorption originating from
  - Different particle sizes (budesonide)
  - Difference in API manufacturing method (UMAX and DISCUS manufacturing of budesonide)

- Dissolv*It* detects similarities in dissolution/absorption as expected for
  - Brand name and generic product (budesonide and formoterol from Symbicort Turbohaler and Bufomix Easyhaler)

- Dissolv*It* generates concentration curves as well as cumulative absorption of FP and Sal in Seretide Evohaler (250/25) very similar to those generated in IPL.

- **Ample evidence that Dissolv*It* can correctly detect potential differences in dissolution/absorption profiles originating in alterations of the test formulations. Dissolv*It* also has the potential to generate data that can be used to predict clinical plasma profiles.**

Acknowledgement

- FDA
- pharm-analyt (LC-MS/MS analysis)
- Karolinska Institutet (SEM images)
- Emmace (development of Mimetikos Preludium module and PBB modeling)

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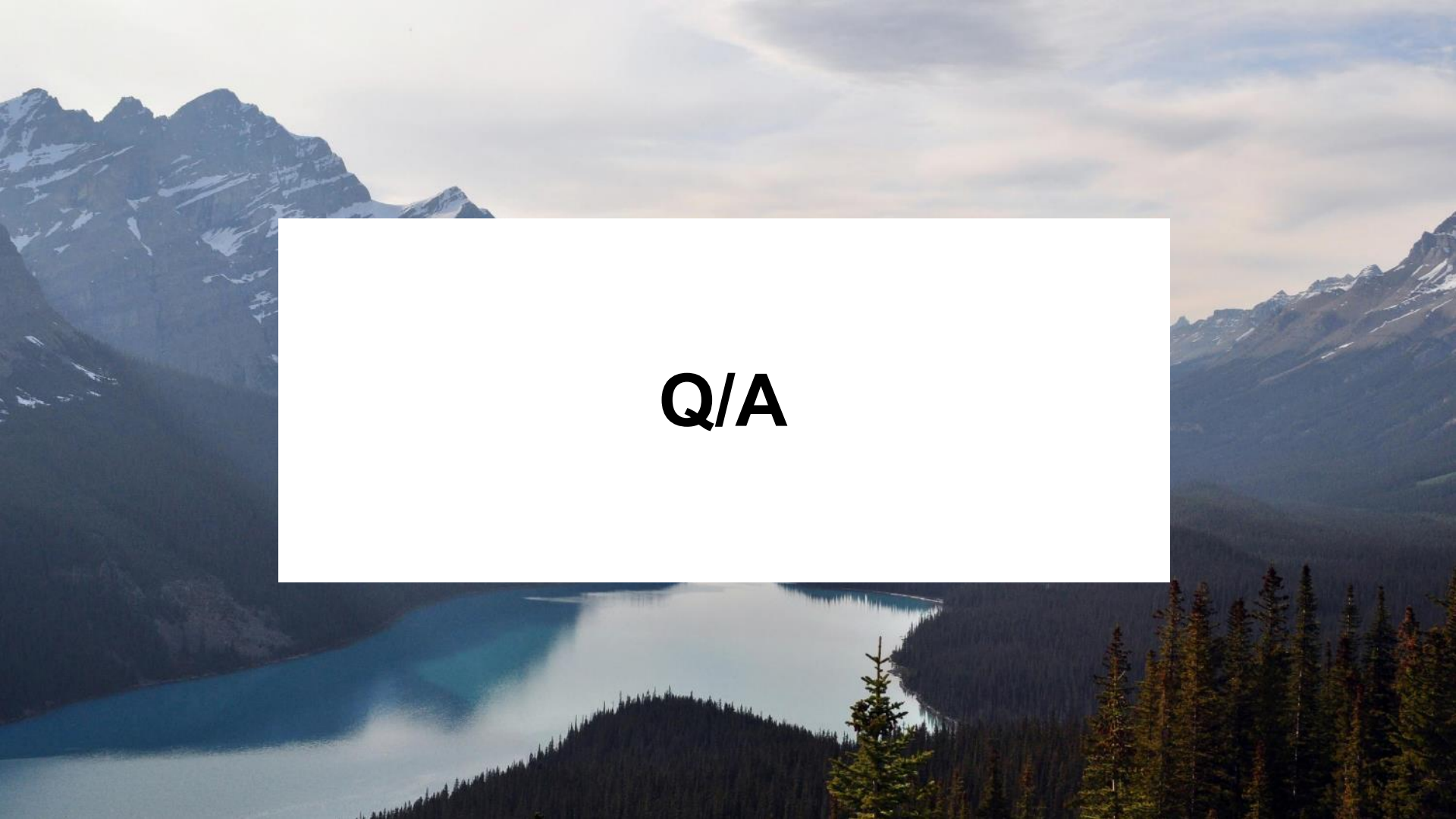
Q/A