Characterizing the time-course of lung absorption via Population Pharmacokinetic Modeling

A new approach to obtain information on the regional deposition of Fluticasone Propionate

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Background

- US market lacks generic inhalation drugs.
- Main reason: FDA recommends *weight-of-evidence* approach, which includes clinical studies
- What needs to be shown:
  - What is the available lung dose?
  - How long does drug stay in the lung?
  - What is the regional deposition?
- Hypothesis: **PK can serve as corner stone for approval process**

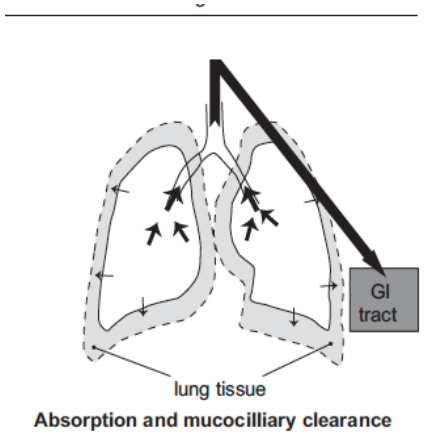
Study Aim

To investigate for slowly dissolving inhalation drugs whether pharmacokinetic studies are sensitive to differences in

- Lung Dose
- Residence Time
- Regional Deposition

Why did we propose that PK can detect differences in c/p

Proposed mechanisms:



Absorption and mucocilliary clearance

- Mucociliary clearance from central regions
  - Assume same lung dose:

    The formulation that delivers more drug centrally will have a smaller AUC

- Slower absorption from more central regions
  - PopPK will be able to identify differences in central and peripheral deposited doses for formulations that differ in c/p ratio

Study design and in-vitro experiments

Manufacturing of 3 Formulations → Characterizing via *in-vitro* studies → Performing PK study → Evaluate study outcome

Manufacturing of 3 **Formulations**

- Different regional deposition
- Same deposited lung dose
- Same dissolution rate

A-4.5 µm
B-3.8 µm
C-3.7 µm

Developed by Dr. Jag Shur and Dr. Robert Price's group at University of Bath (UK)

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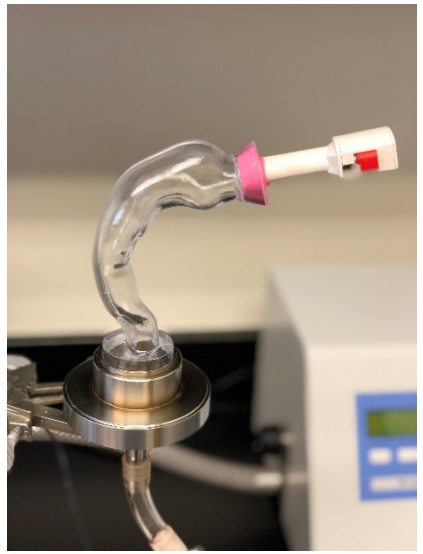
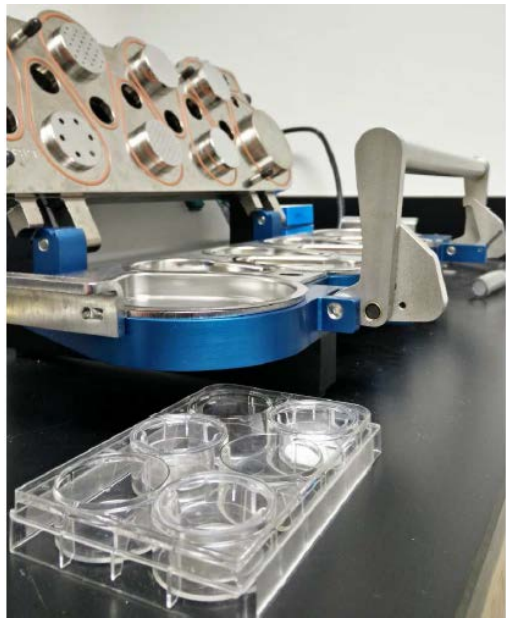
Study design and in-vitro experiments

Manufacturing of 3 Formulations → **Characterizing via *in-vitro* studies** → Performing PK study → Evaluate study outcome

Characterizing via ***in-vitro* studies**:

- Standard cascade impactor studies
- Anatomical throat, inhalation profiles
- Dissolution





Developed by Dr. Güenther Hocchaus's group at University of Florida (US)
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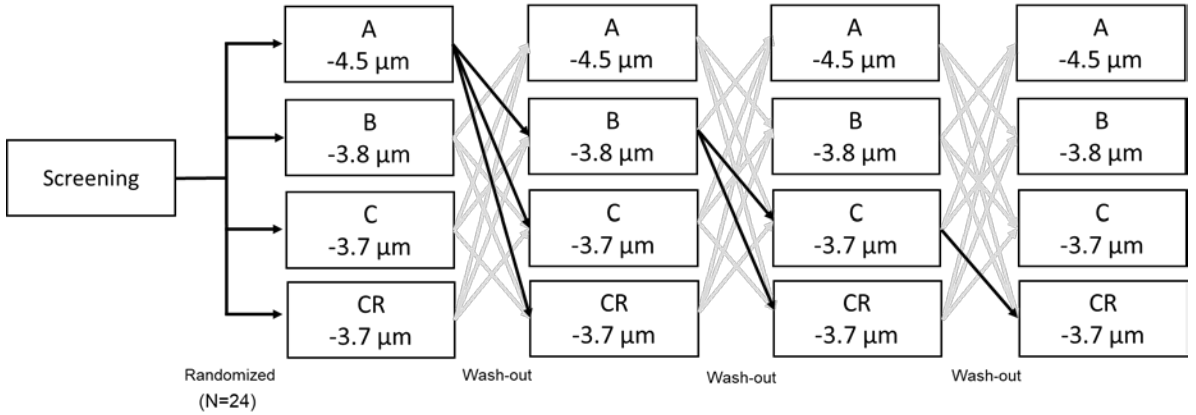
Study design and in-vitro experiments

Manufacturing of 3 Formulations → Characterizing via in-vitro studies → **Performing PK study** → Evaluate study outcome

Performing PK study

- Standardization and in-depth training of inhalation technique
- Single-dose, double-blinded, four-way, crossover clinical study in 24 healthy subjects
- Formulation C was given twice (C and $C_{Reference}$) to assess intra subject variability
- Blood samples were obtained at pre-dose ad up to 24 hours after dosing



Study design and in-vitro experiments

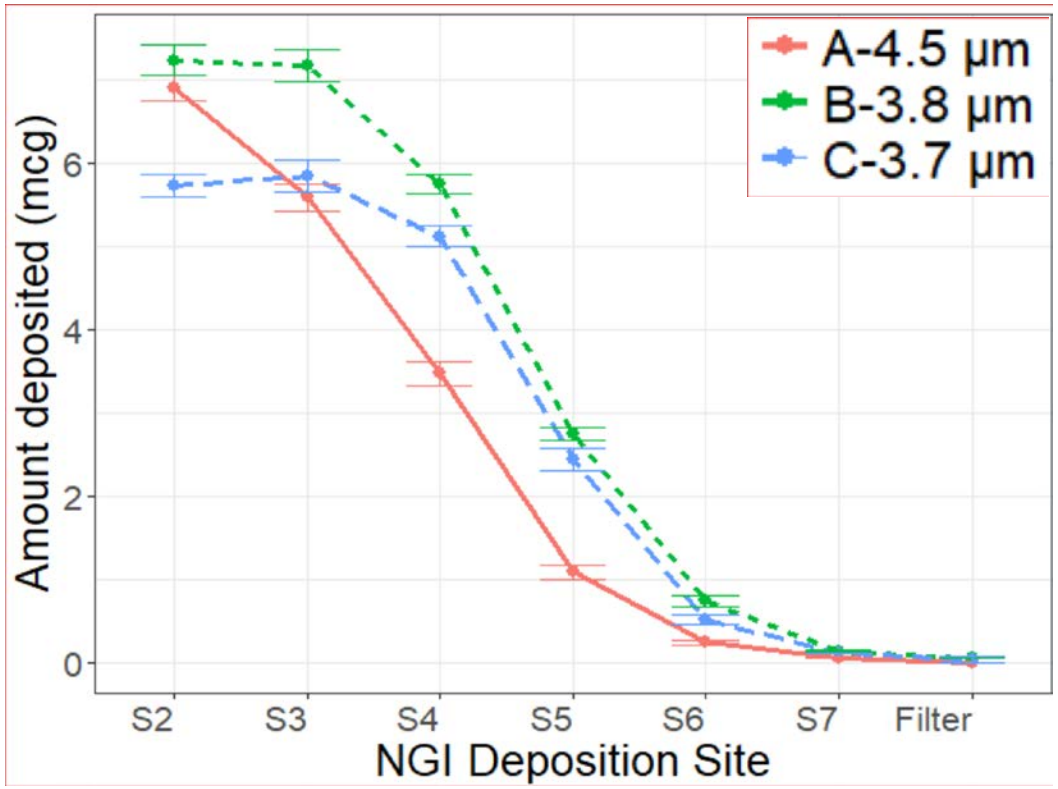
Evaluate study outcome

- Non Compartmental Analysis
- Compartmental Analysis:

  Modeling was performed in S-ADAPT software (version 1.57) using the "importance sampling" algorithm

Formulation characteristics and *in-vitro* results

Cascade impactor performance



	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
FPD < 5µm (µg)	12.2	18.7	15.8
FPD < 3µm (µg)	5.3	10.0	8.6
Stage 2 to 3 (µg)	12.5	14.4	11.5
Stage 4 to 7 (µg)	4.8	9.4	8.1

- Similar mass deposition on Stage 2 to 3
- Mass deposition in stage 4-7 was substantially smaller for A-4.5 µm
- A-4.5 µm had slowest in vitro dissolution rate (data not shown here)

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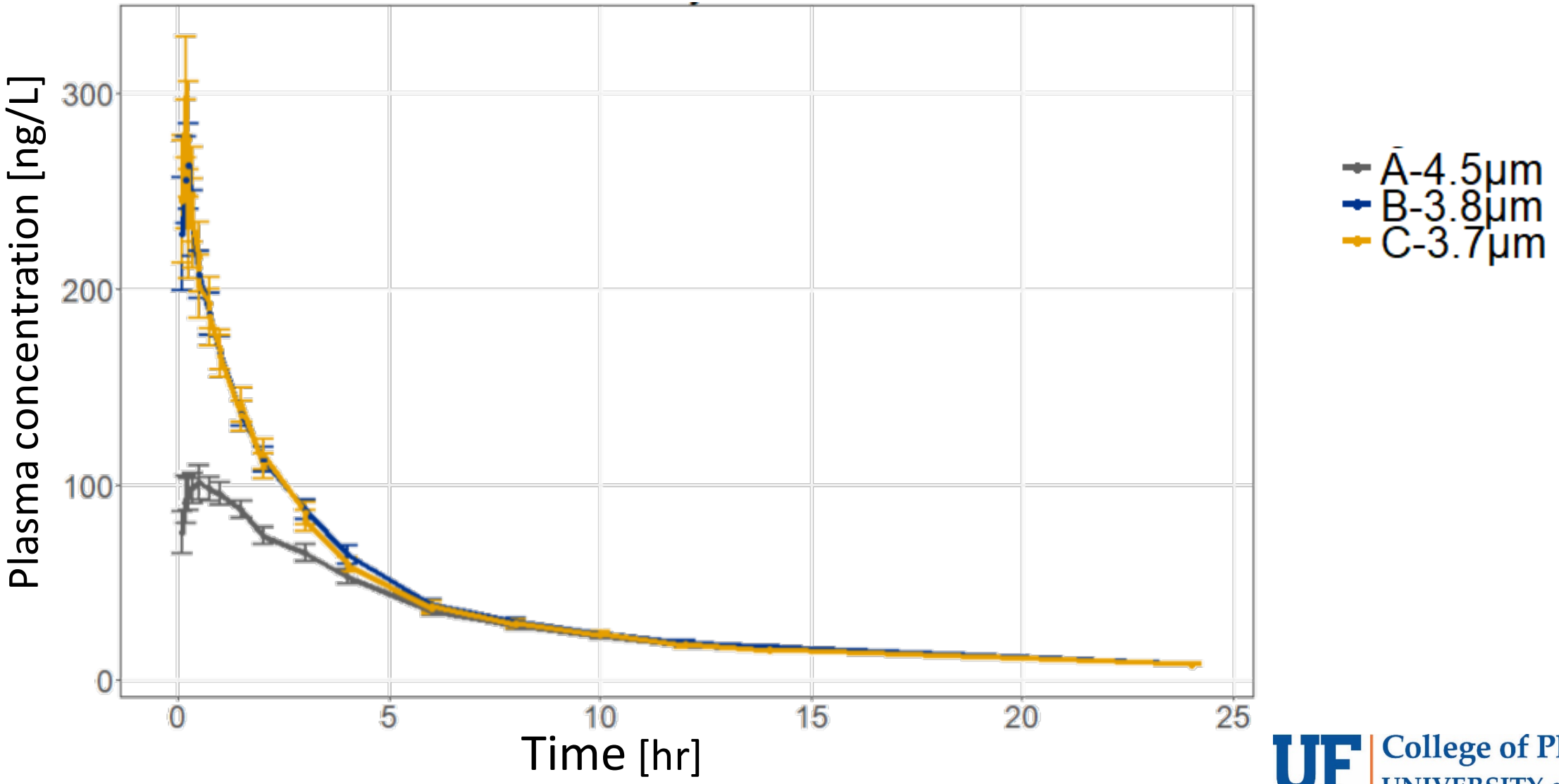
Median (±SE) PK Profile



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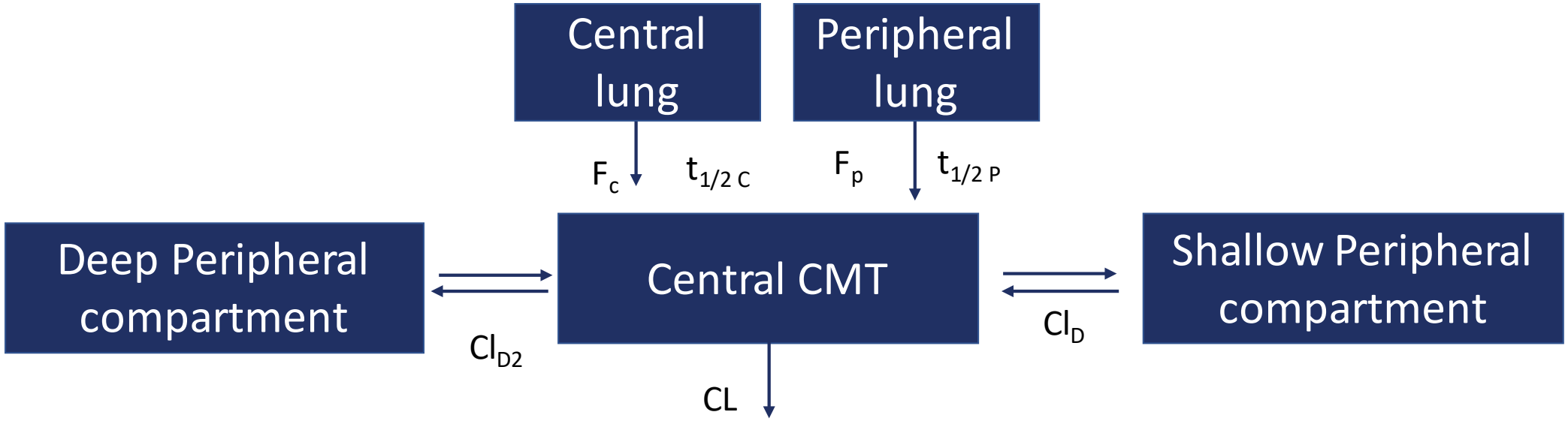
Model structure

F_c: Absorbed dose fraction from central lung
F_p: Absorbed dose fraction from peripheral lung
$t_{1/2\,C}$: Absorption half life from central lung
$t_{1/2\,P}$: Absorption half life from peripheral lung



- Two parallel first-order absorption processes from the central lung (slow) and peripheral lung (fast)
- Total clearance (CL) informed by published IV PK data
- Separate F_c, F_p, $t_{1/2\,C}$, $t_{1/2\,P}$ estimated for **each** formulation

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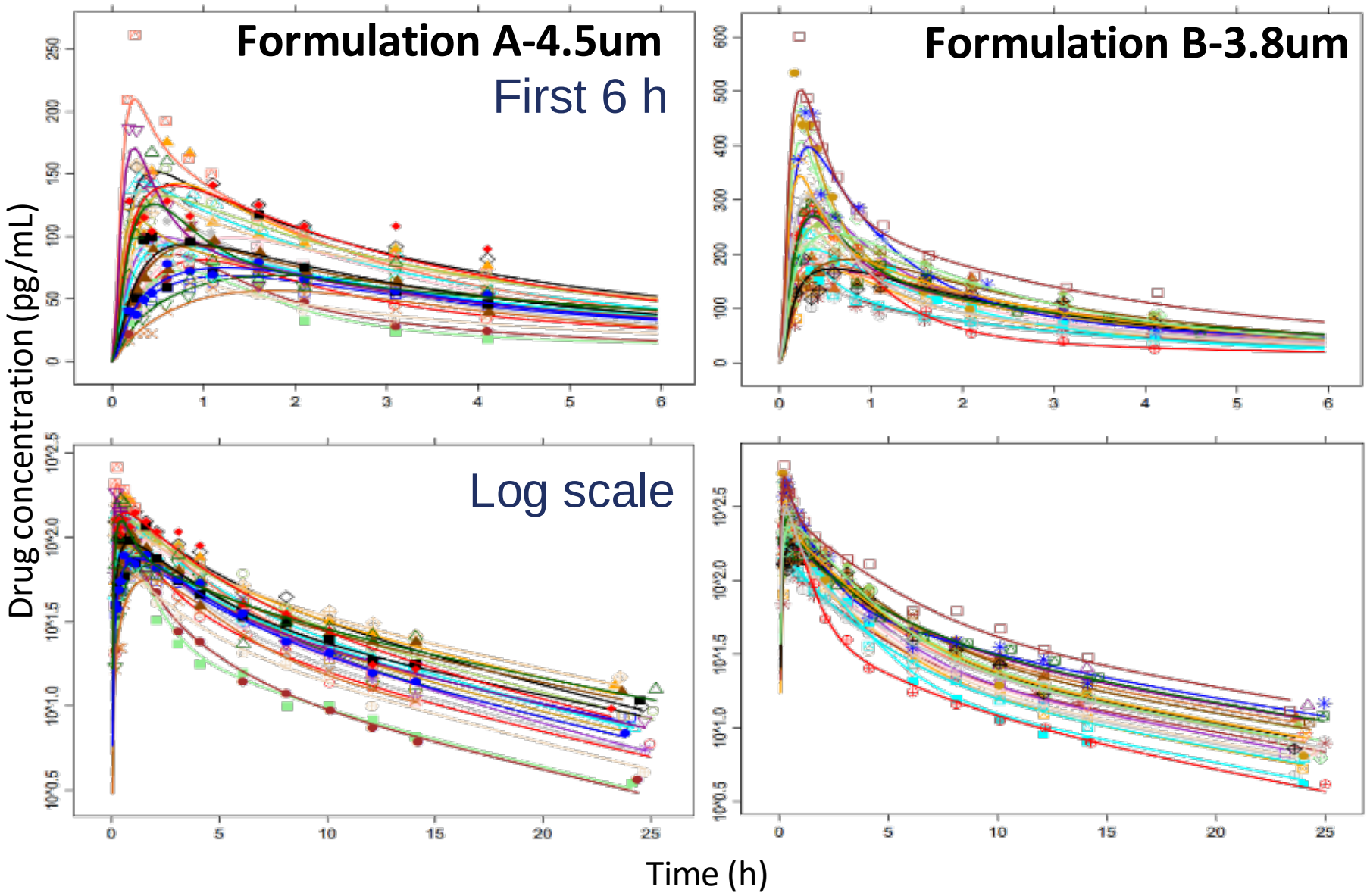
Model structure



Similarly excellent curve fits for formulation C.

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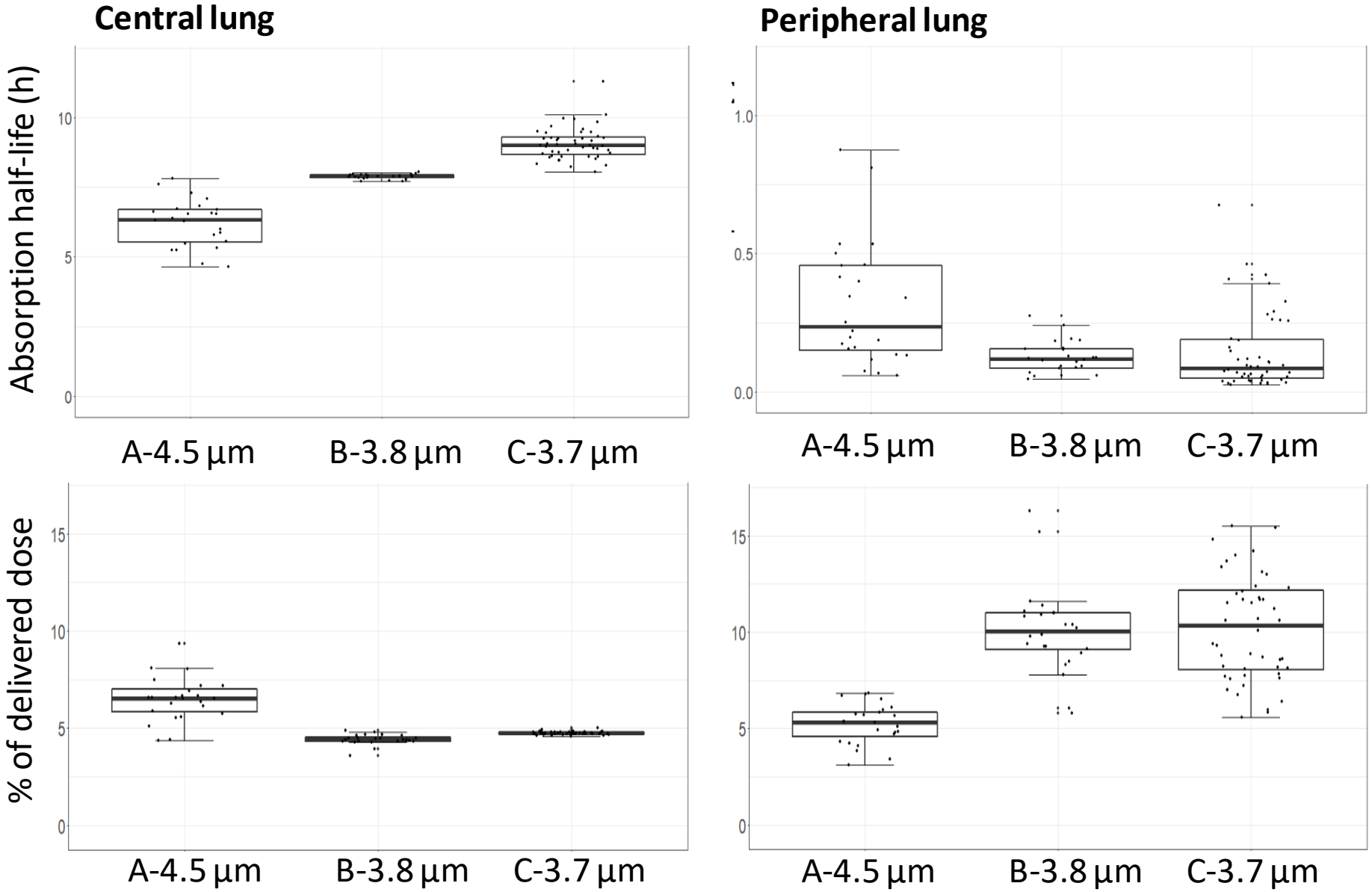
Lung specific PK parameter estimates



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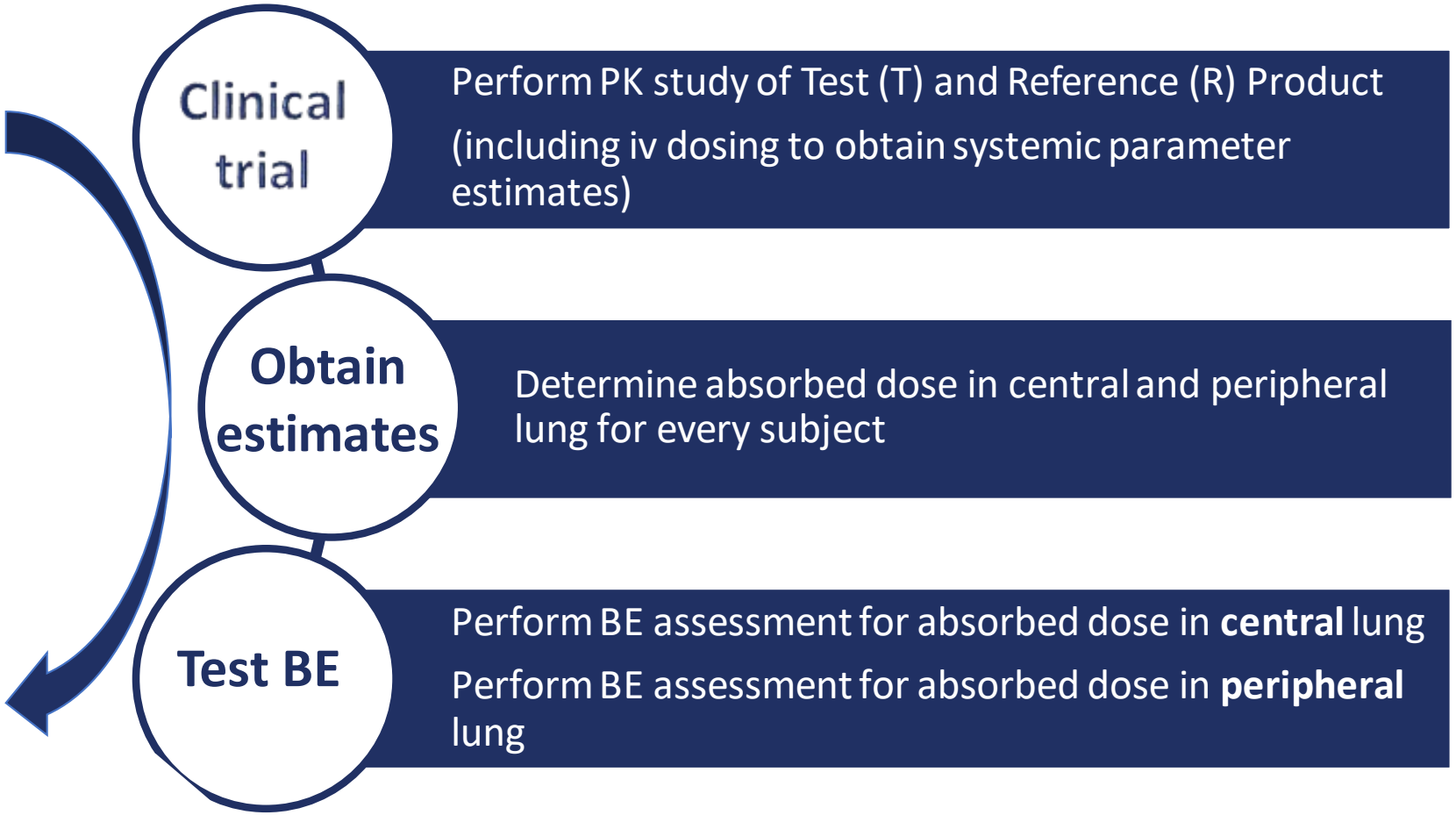
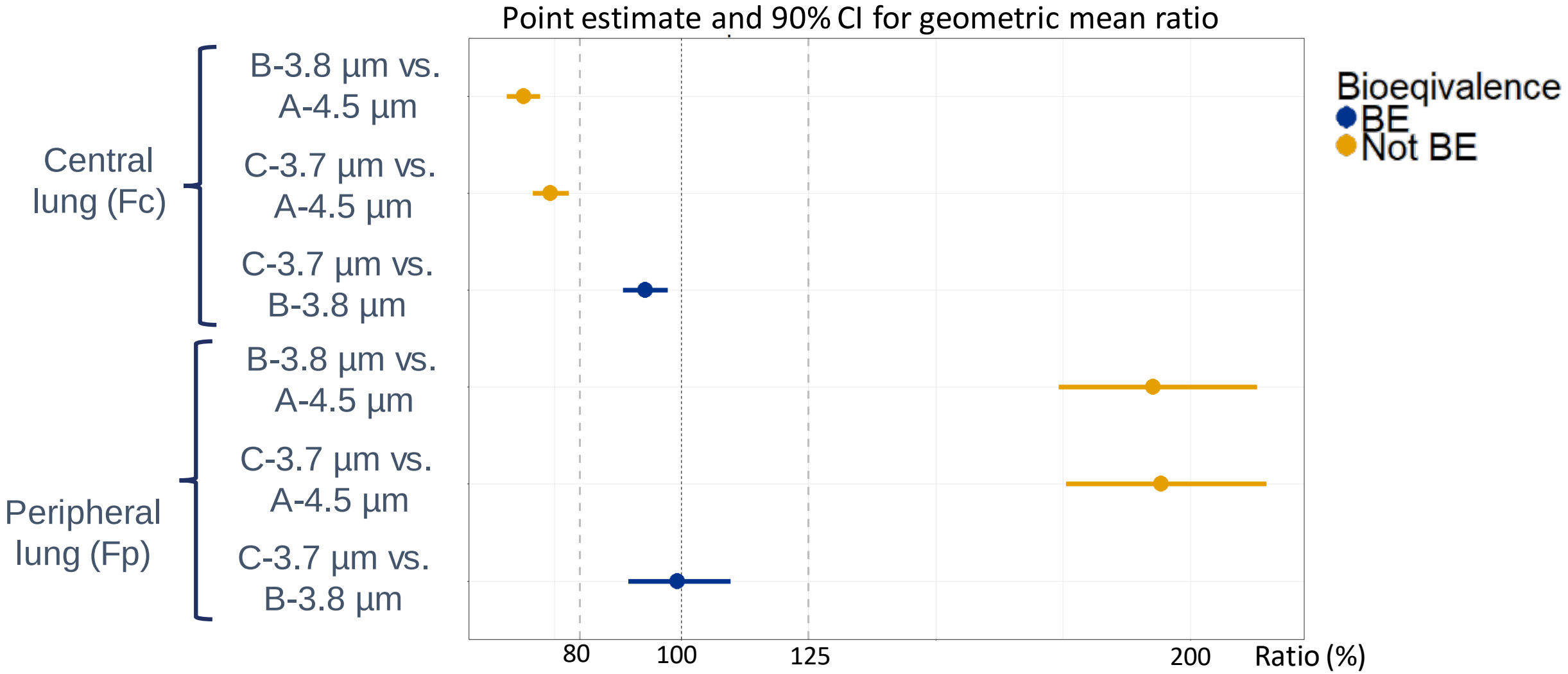
Proposed new Methodology for PopPK BE testing



PopPK parameters BE Approach



- B-3.8 µm and C-3.7 µm were bioequivalent for both F_c and F_p
- A-4.5 µm vs B-3.8 µm and A-4.5 µm vs. C-3.7 µm were not bioequivalent

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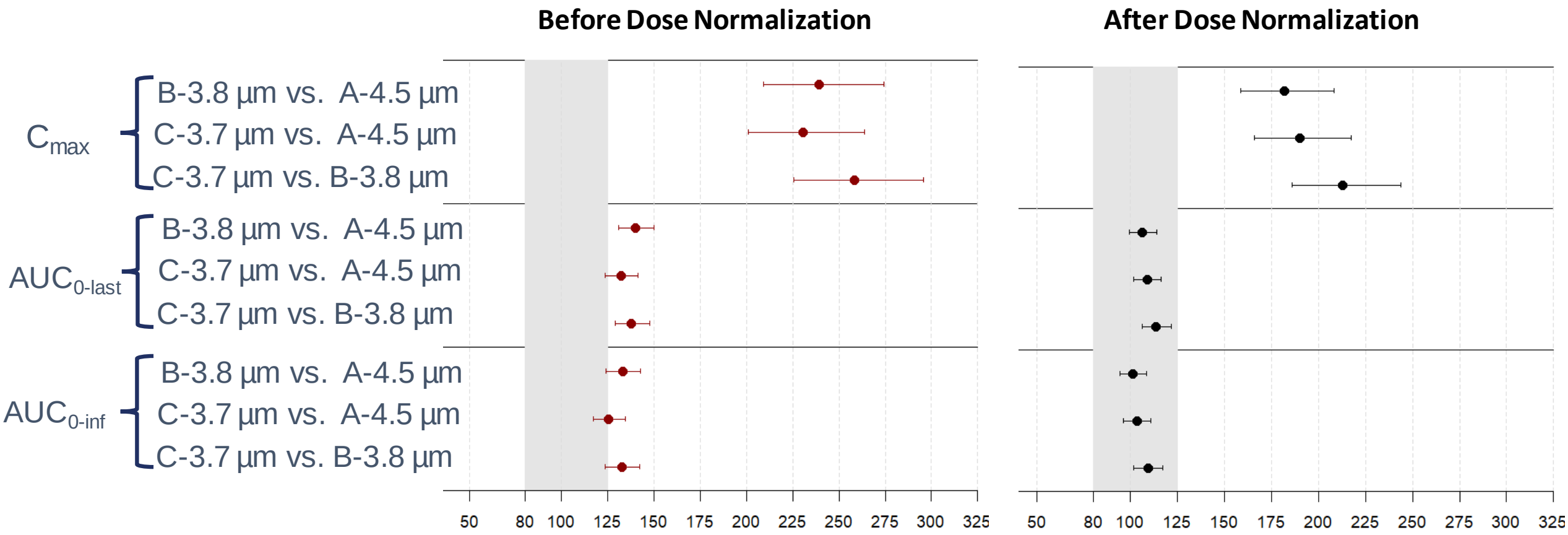
Results from NCA



- PK can detect difference in pulmonary dose (AUC before dose normalization)
- PK can differentiate slower rate of absorption (C_{max})

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Conclusion

PopPK may be able to provide information on c/p ratio for slowly dissolving drugs.

- NCA able to compare T and R for "available lung dose" and "residence time".
- PopPK could further distinguish between drug (FP) absorbed from central (slow) and peripheral (fast) lung.
- PopPK and NCA offer complementary insights and both should be considered for BE testing of inhaled drugs with bi-phasic lung absorption.

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Thank you

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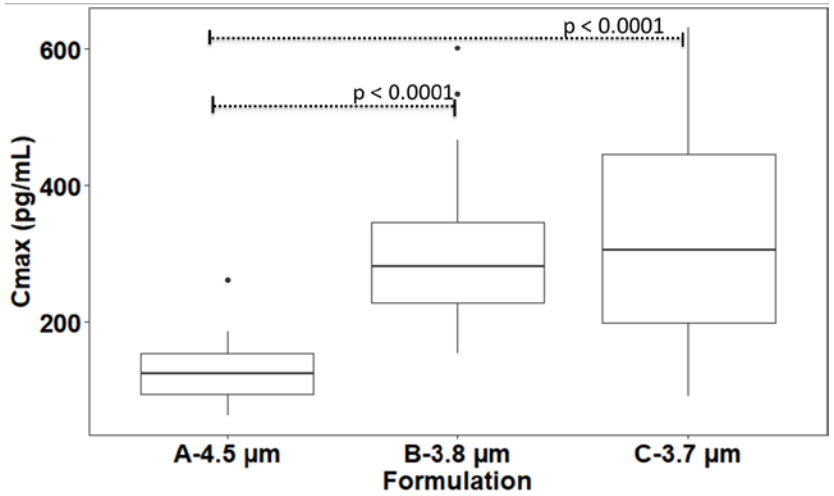
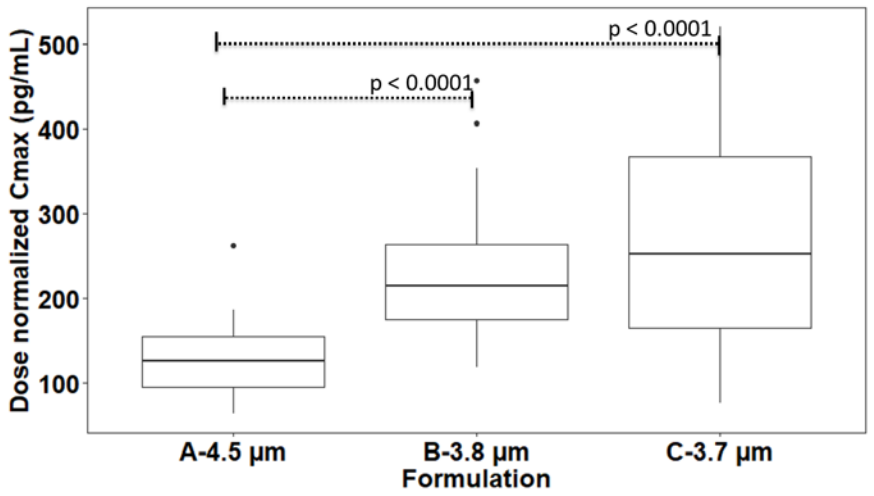
BACKUP SLIDES

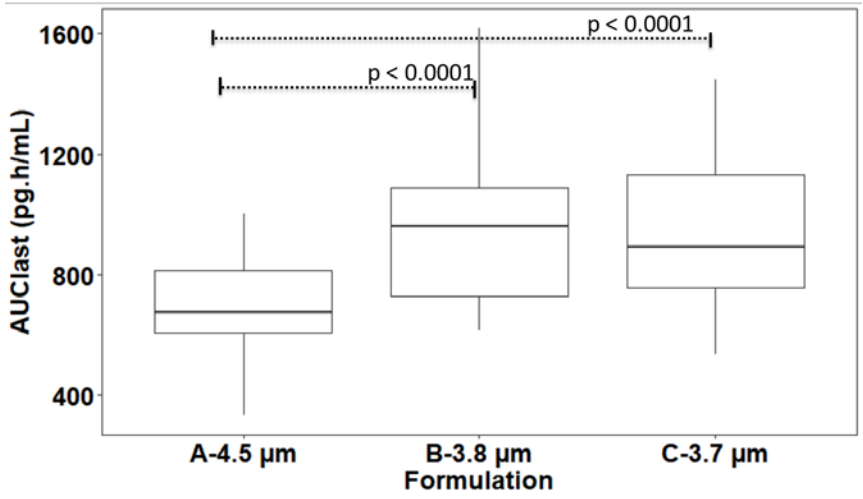
Results from statistical testing

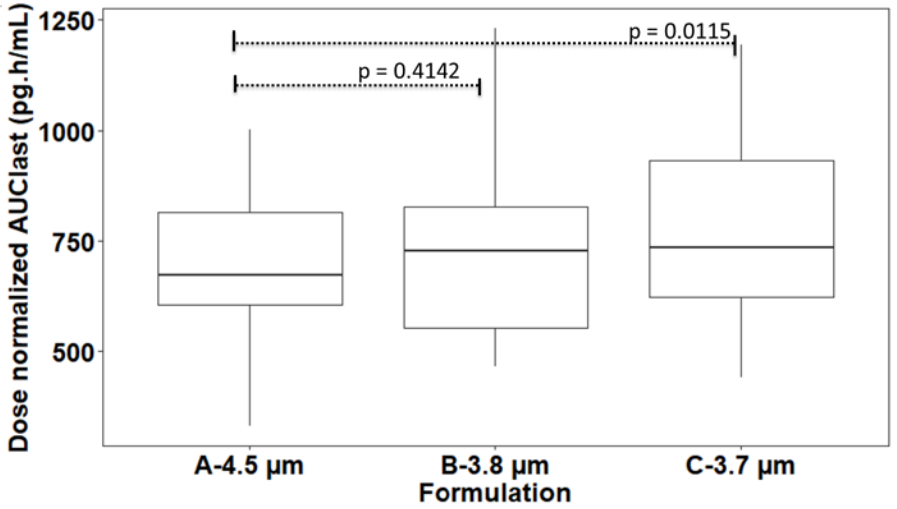
Before Dose Normalization



After Dose Normalization







The total lung dose and absorption rate of Formulation A might be smaller compared to Formulation B and C

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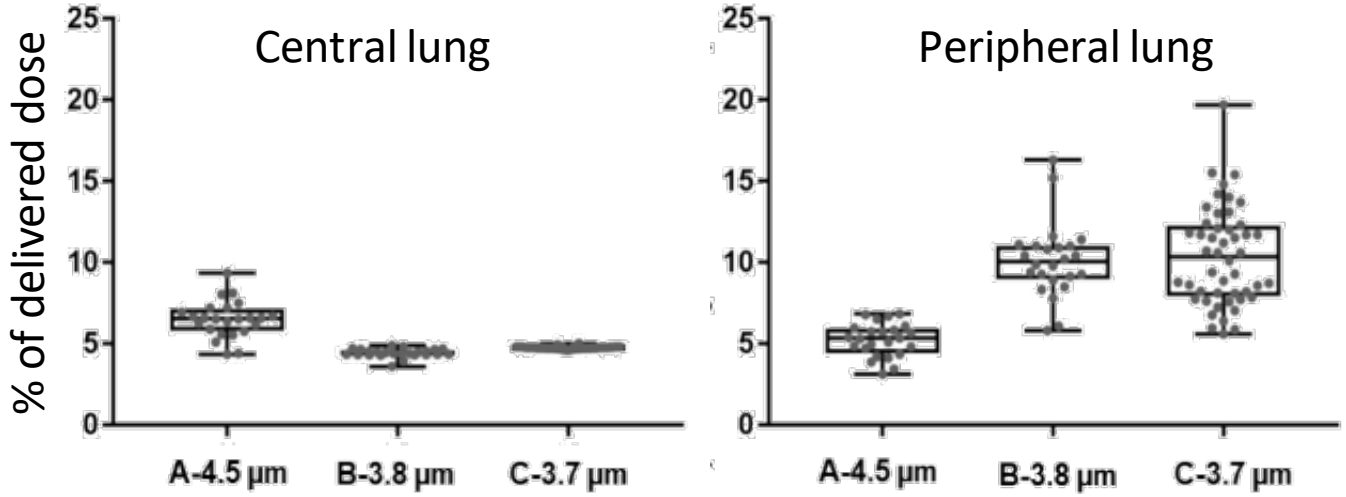
Population mean PK parameters and between subject variability estimates

Parameters	Symbol	Unit	Formulation A	Formulation B	Formulation C
			Mean (SE%)[a]	Mean (SE%)[a]	Mean (SE%)[a]
Absorption half-life for central lung	$t_{1/2\_c}$	h	6.2 (13.1%)	7.9 (46.1%)	9.1 (18.4%)
Absorption half-life for peripheral lung	$t_{1/2\_p}$	h	0.241 (18.7%)	0.114 (35%)	0.096 (19.3%)
Absorbed dose from central lung	**F_c**	**%**	**6.4 (18.2%)**	**4.4 (19.9%)**	**4.8 (15.1%)**
Absorbed dose from peripheral lung	**F_p**	**%**	**5.1 (13%)**	**9.9 (17.1%)**	**9.9 (11.3%)**



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