Feasibility of predicting regional lung exposure from systemic pharmacokinetic (PK) data of generic OIDPs via population PK

Jürgen Bulitta and Günther Hochhaus

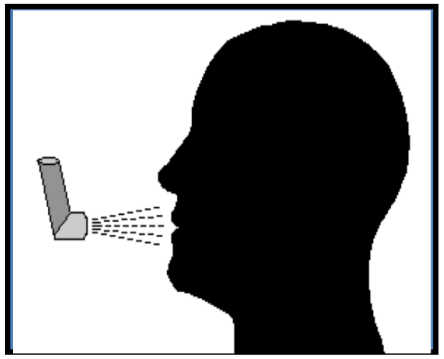
Based on our collaboration on the Fluticasone Propionate DPI study with

Rob Price, Jag Shur (Univ. of Bath)
Mike Hindle (VCU)
Worldwide Clinical Trials (bioanalysis)

UF UNIVERSITY of FLORIDA

FDA public Workshop :
Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products

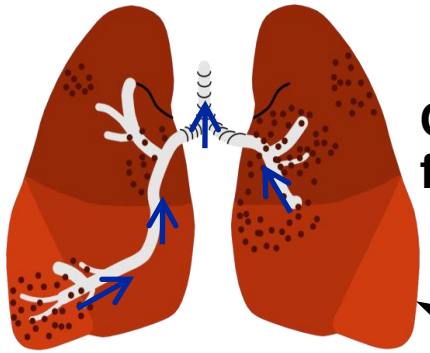
Topics related to Bioequivalence



Mouth and pharynx

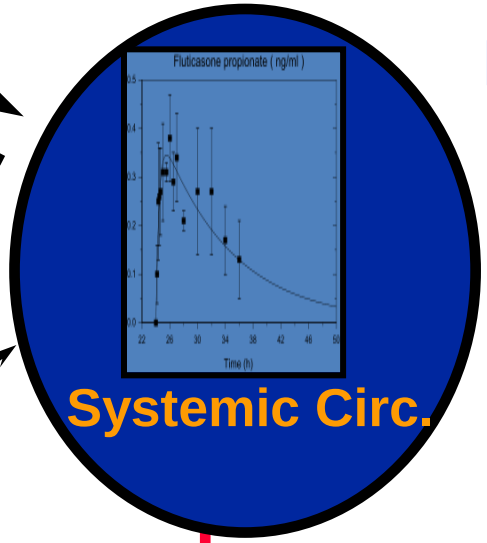
10 - 60 %
Deposited
in lung

Cl_{muc}

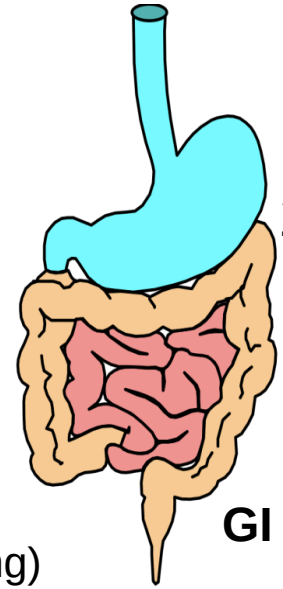


Lung

Complete absorption
from the lung

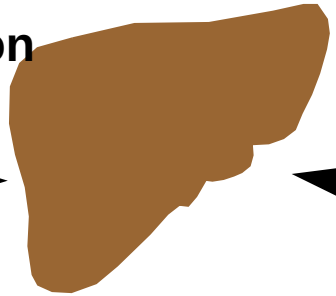


Orally bioavailable
fraction



GI tract

Absorption
from gut



Liver

First-pass
inactivation

Systemic
side effects

40 - 90 %
Swallowed
(reduced by
spacer
or mouth rinsing)

For this talk, **no gastro-intestinal absorption**.
Low oral F (e.g. due to high first-pass metabolism), or blocked via charcoal (for other drugs).

Benefit of and how to handle IV PK

Overarching questions

Can a PK study assess pulmonary bioequivalence?

What does population PK add? **How to robustly implement it?**

Specifically:	**NCA**	**PopPK**
1. What is the dose available to the lung?	Yes (AUC)	Yes (Ac + Ap)
2. How long does the drug stay in the lung?	Yes (Cmax, mean residence time)	(Yes; lung absorption half-lives)
3. What is the central to peripheral (C/P) drug deposition ratio in the lung?	(Yes) (Cmax) Depends on situation	Yes (Ac, Ap) if bi-phasic absorption

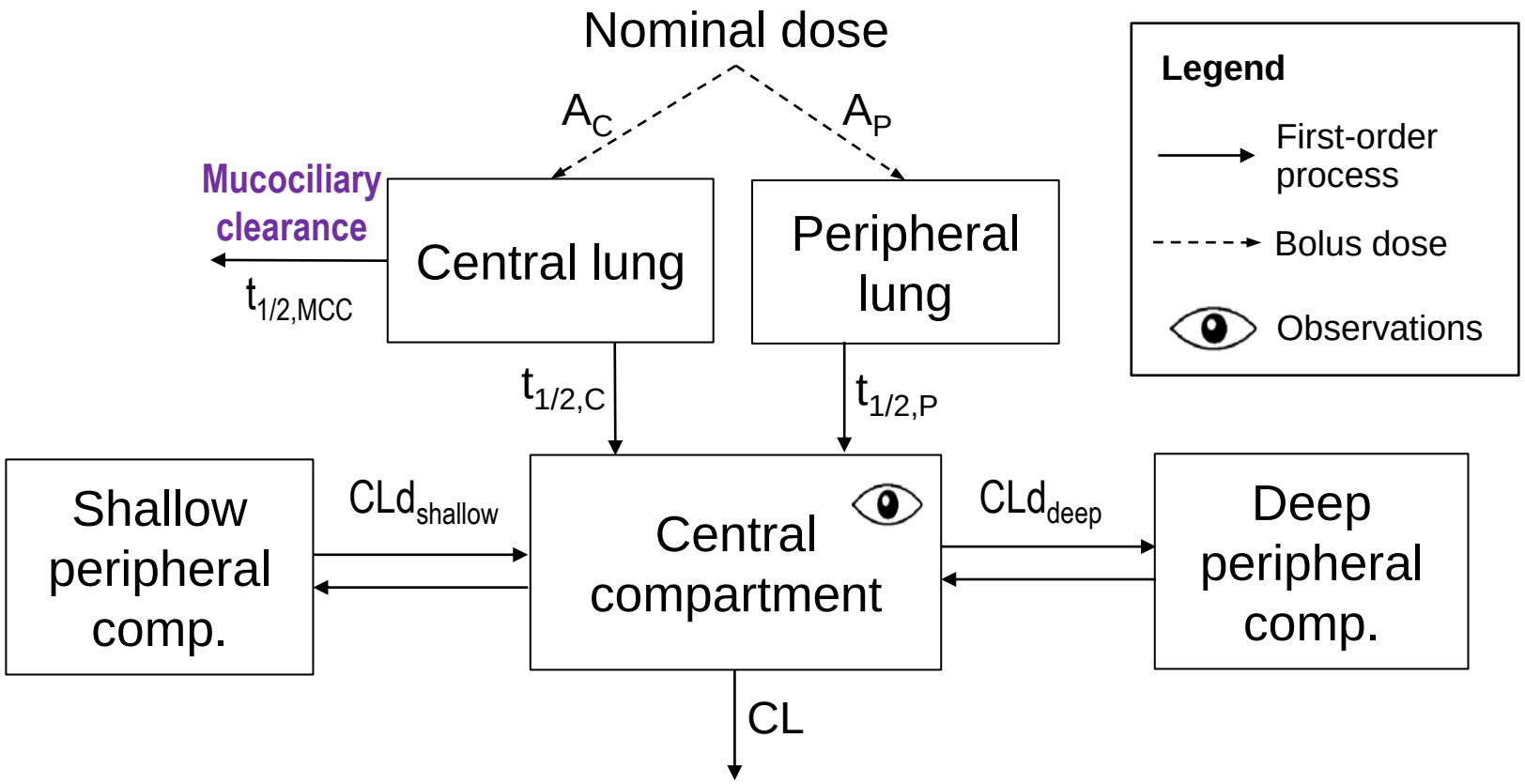
Ac: Amount of drug deposited in central lung (partially absorbed, due to mucociliary clearance).
Ap: Amount of drug deposited in and absorbed from peripheral lung (no mucociliary clearance).
CL: Total clearance (e.g. from IV data), Cmax: Peak plasma concentration, AUC: Area under the curve in plasma.

Hypothesis and Model for Fluticasone Propionate

For slowly dissolving drugs, PK should allow one to assess differences in:

- **Lung dose**
- **Lung residence time** (absorption)
- **Regional deposition** (more central deposited drug will be removed more efficiently by mucociliary clearance)

- Oral absorption assumed to be absent (F_{oral} <1%)
- No charcoal used for FP.
- No IV treatment arm in our clinical study.



Drescher SK et al. “PopPK of Fluticasone Propionate”. Pharm Res 2023 (in press).

Goal of Original PK Study

Probe whether PK is sensitive to differences in the c/p ratio for slowly dissolving drugs (FP).

- **Develop three DPI-FP formulations. If possible:**
  - Same dose
  - Same dissolution rate
  - Difference in central to peripheral lung deposition.
  - Different lactose fines, FP powder same for all formulations
- **Characterize through in vitro experiments**
- **Perform human PK study** (4 way cross-over, repeat one formulation to assess intra-individual variability)

Formulation Work

(Dr. Jag Shur, Robert Price, Univ of Bath)

3 formulations only differing in lactose fines

Product Name	Formulation (% w/w)	Lot Number
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 96.72 Lactohale LH300: 2.48	C-3.7µm Labelled as 15MM-015 In Appendixes
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 79.36 Lactohale LH201: 19.84	A-4.5µm Labelled as 15MM-017 In Appendixes
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 89.28 Lactohale LH230: 9.92	B-3.8µm Labelled as 15MM-016 In Appendixes

Hochhaus G et al. “NCA PK of FP”. AAPS J 2021; 23:48.

APSD deposition profiles from compendial NGI in vitro testing

c/p ratio (Preludium)

A-4.5 µm : 0.83
B-3.8 µm : 0.64
C-3.7 µm : 0.66

	A-4.5 µm	B-3.8 µm	C-3.7 µm
Stage 2 to 3 (µg)	12.48	14.40	11.54
Stage 4 to 7 (µg)	4.83	9.37	8.14

Similar → mucociliary CL may have similar impact

Different

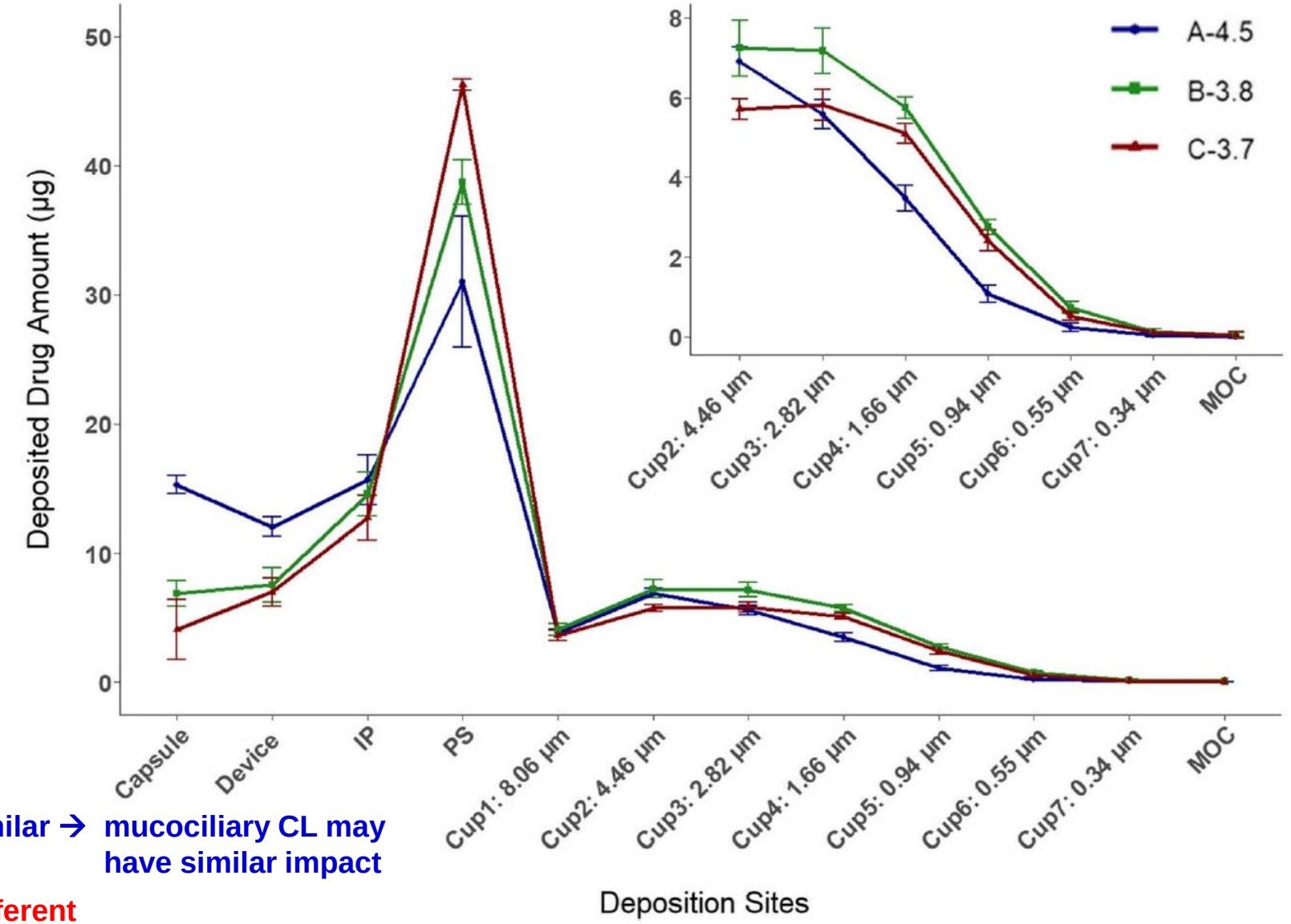


Figure 1. APSD deposition profiles from compendial NGI *in vitro* testing (mean ± standard deviation of at least 5 replicates; data combined from samples stored from 12 to 20 months at ambient conditions (25°C; 60% RH) which is a good representation of the FP DPI formulations administered in the PK study). IP, induction port; PS, pre-separator; MOC, micro-orifice collector

Hochhaus G et al. "NCA PK of FP". AAPS J 2021; 23:48.

Do formulations provide same absorption rate?

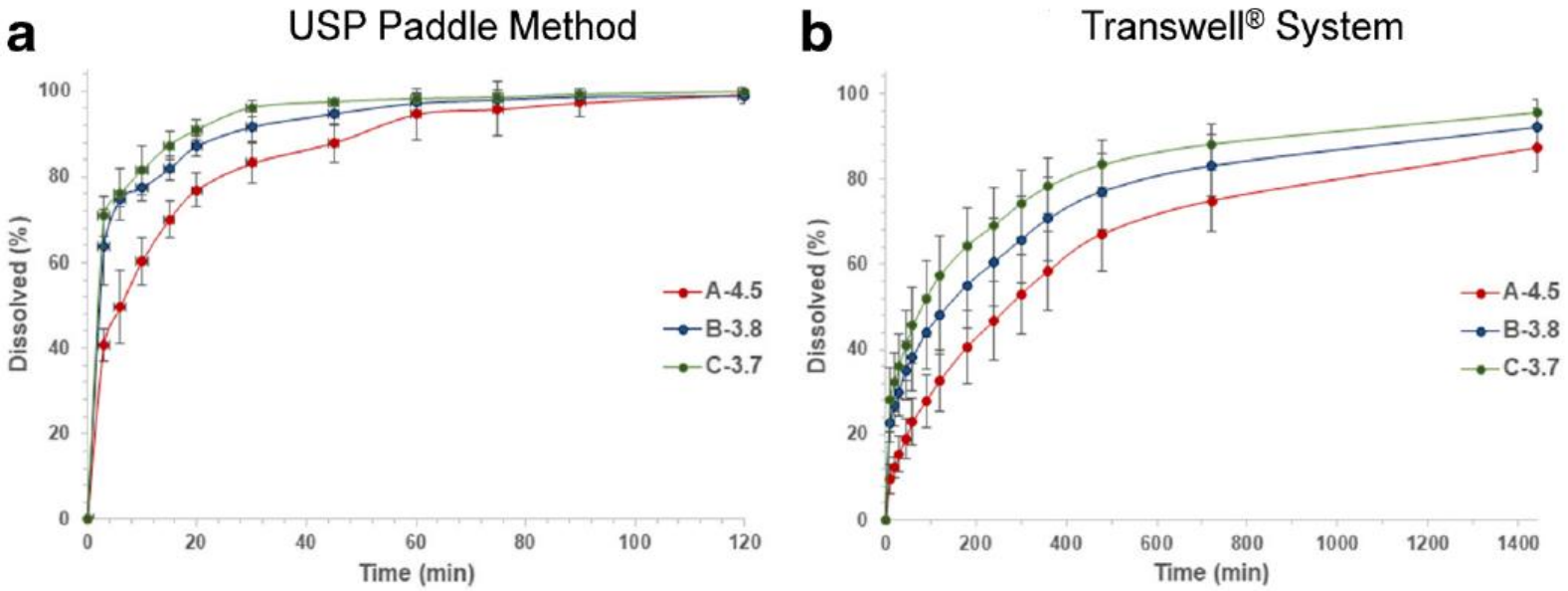
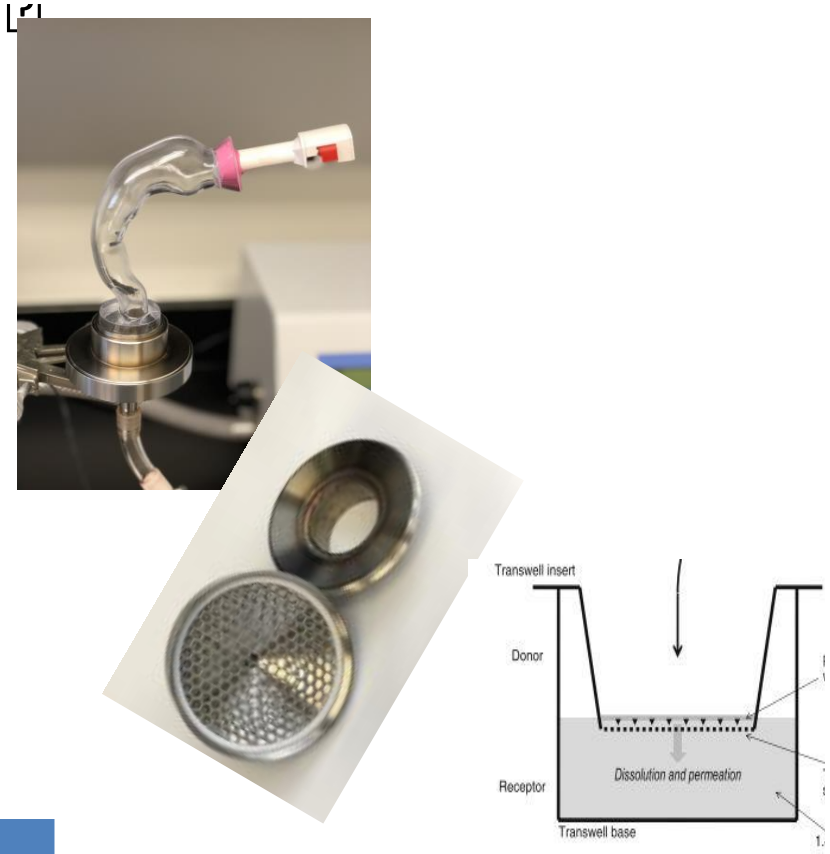


Figure 2. Dissolution of FP DPI formulations. Percent dissolved (mean ± standard deviation) of FP DPI formulations A-4.5, B-3.8, and C-3.7 using either the USP paddle apparatus (**a**) or the Transwell® system (**b**)



Arora, D., (2010)

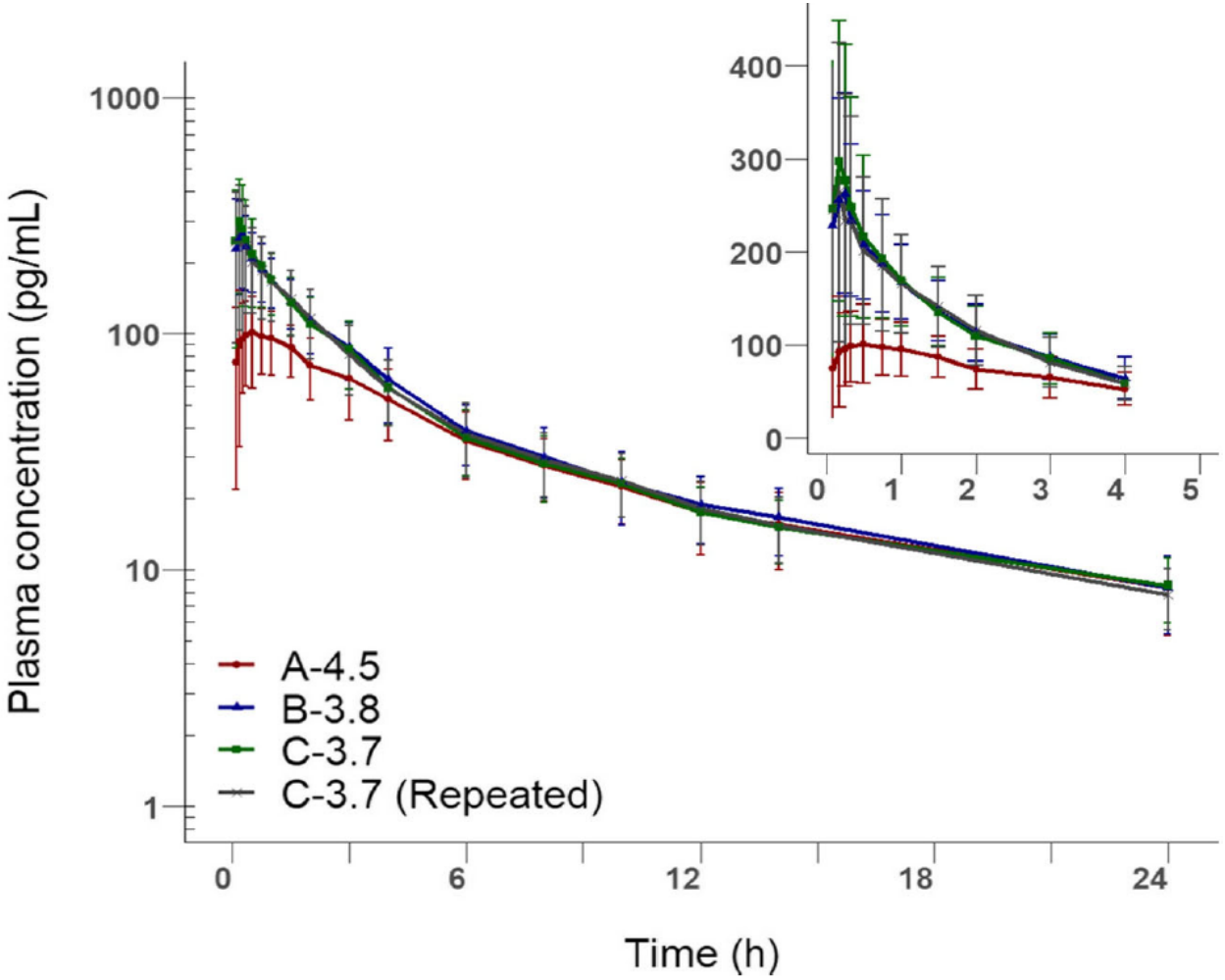
Formulation	Parameter	Value
A-4.5 µm	MDT	15.4 h
B-3.9 µm	MDT	13.3 h
C-3.7 µm	MDT	10.3 h

Hochhaus G et al. AAPS J 2021; 23:48.

PK Study Design

- 4-way, cross-over, double blind in 24 healthy volunteers
  DPI formulations with Plastiape: A-4.5 µm, B-3.8 µm,
  C-3.7 µm, and CR-3.7 µm (repeat to inform intra-subject variability)
- Dose: 5x 100 µg fluticasone propionate
- Recorded individual inhalation profiles
- LC-MS/MS Assay sensitivity: 1 pg/mL (Worldwide Clinical Trials, TX)
- Non-compartmental Analysis +
  Compartmental Population PK Analysis

Concentration time profiles for FP used for popPK modeling

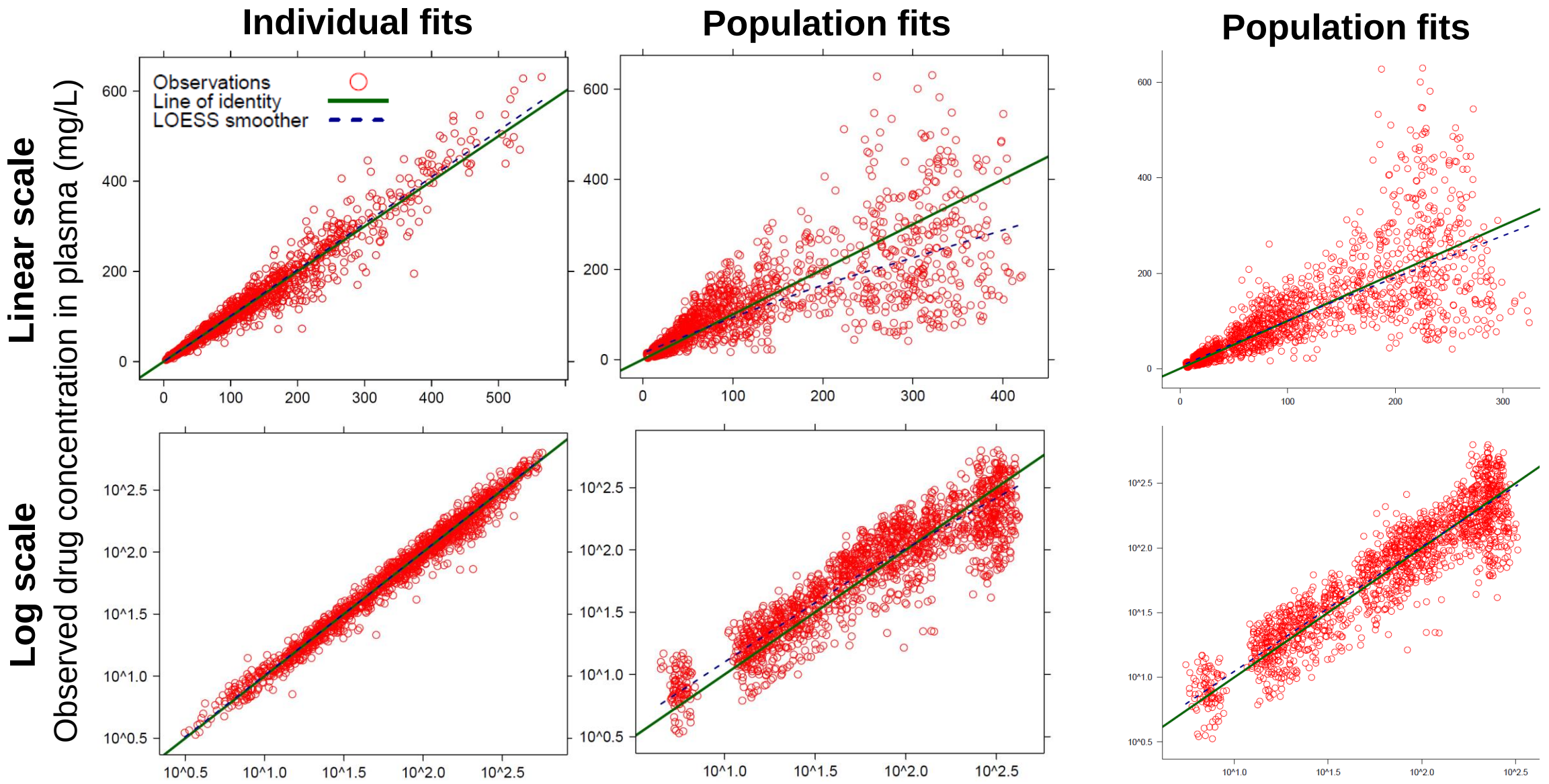


→ Terminal half-life (10 h) was independent of formulation.

→ Formulation A-4.5 µm had lower peak concentrations (both before and after dose normalization).

Hochhaus G et al. AAPS J 2021; 23:48.

Curve fits: Model **with** IV data from literature **without** IV data



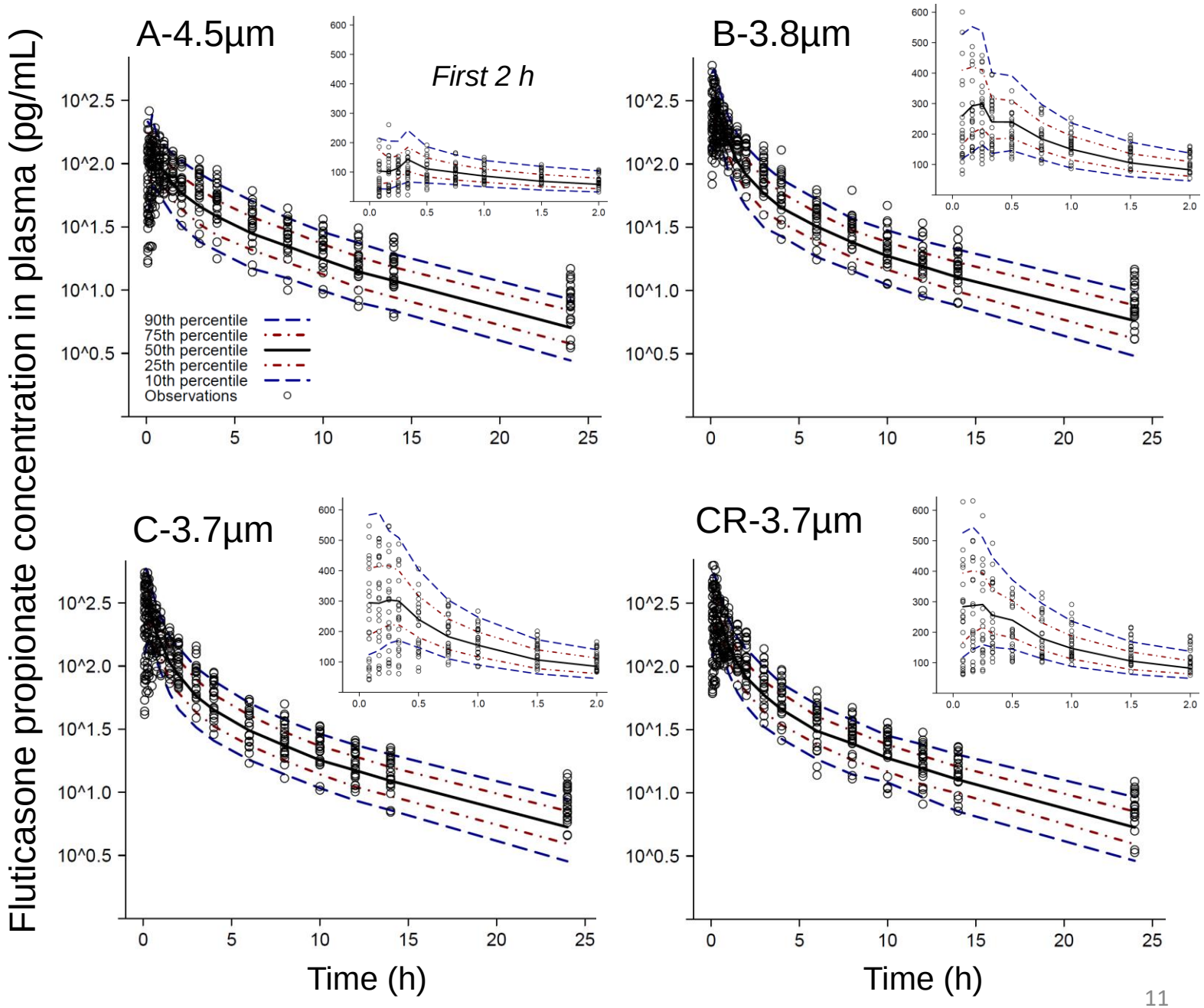
Drescher SK et al.
Pharm Res 2023 (in press).

Visual predictive check

Population PK model adequately captured the central tendency and between subject variability of the observations.

Model with 2 vs. 1 pulmonary absorption processes was substantially and clearly superior (-2x log-likelihood better by 747 [503 to 940]).

This was confirmed in 200 of 200 bootstrap replicates, and 100 replicates in another study.



Drescher SK et al.
Pharm Res 2023 (in press).

Bioequivalence results for the ratio of geometric means based on individual (POSTHOC) parameter estimates from population PK modeling

Parameter	Test	Reference	Test/Ref ratio (%)	Lower 90% CI (%)	Upper 90% CI (%)
Total Dose Deposited C+P[a]	A	CR	98.46	92.10	105.25
	B	CR	106.03	99.19	113.35
	C	CR	100.57	93.39	108.30
Dose Deposited in central lung[b]	A	CR	170.64	158.23	184.02
	B	CR	115.85	107.43	124.94
	C	CR	101.95	93.76	110.85
Dose Absorbed from peripheral lung[b]	A	CR	33.24	29.20	37.83
	B	CR	96.81	85.06	110.19
	C	CR	98.10	84.97	113.25
C/(C+P) ratio for Deposited Dose[b]	A	CR	173.31	160.82	186.78
	B	CR	109.26	101.38	117.75
	C	CR	101.37	93.30	110.15

Formulations B, C and CR (i.e. repeat of C) were bioequivalent.

Formulation A-4.5 µm was bio-IN-equivalent for all comparisons.

→ PopPK can inform ANOVA for BE testing in central and peripheral lung.

→ I.e. popPK could distinguish between both lung regions.

Drescher SK et al. Pharm Res 2023 (in press).

Population mean PK parameters

Parameters	Symbol	Unit	Formulation A	Formulation B	Formulation C
			Mean (SE%)[a]	Mean (SE%)[a]	Mean (SE%)[a]
Mucociliary clearance half-life	$t_{1/2,MUC}$	h		8.44 (fixed)	
Absorption half-life for central lung	$t_{1/2,c}$	h	9.13 (6.9%)	7.17 (46.9%)	6.86 (21.9%)
Absorption half-life for peripheral lung	$t_{1/2,p}$	min	14.6 (25.9%)	6.92 (13.3%)	6.85 (15.0%)
Amount of FP deposited in central lung	**Ac**	**µg**	**61.9 (36.4%)**	**40.5 (21.9%)**	**35.6 (12.4%)**
Amount of FP deposited in and absorbed from peripheral lung	**Ap**	**µg**	**12.6 (16.1%)**	**38.7 (27.1%)**	**39.3 (9.9%)**

Monte Carlo simulation estimation study with four hypothetical formulations

	A	B	C	D
Amount deposited centrally, Ac (µg)	60	40	40	25
Amount deposited peripherally, Ap (µg)	12.5	40	40	55
Amount deposited total Ac + Ap (µg)	72.5	80	80	80
C / (C+P) ratio	**0.83**	**0.5**	**0.5**	**0.31**

Central absorption half-life: **7 h** for all formulations

Peripheral absorption half-life: **7 min** for all formulations

Typical IV disposition half-lives:

$t_{1/2,alpha}$: 13 min, $t_{1/2,beta}$: 1.3 h, $t_{1/2,gamma}$: **10.6 h**

Simulation approach

- Simulate a 5-way cross-over study, with formulations A to D with inhaled FP of 500 µg, plus one 10 min IV infusion at 80 µg.
- Simulate 400 subjects with between subject variability in weight as well as between subject and between occasion variability in PIFR.
- Generate 100 random bootstrap datasets of 24 subjects each.
- Estimate all 100 simulated bootstrap datasets with population PK using 4 different approaches.

Population PK estimation approaches

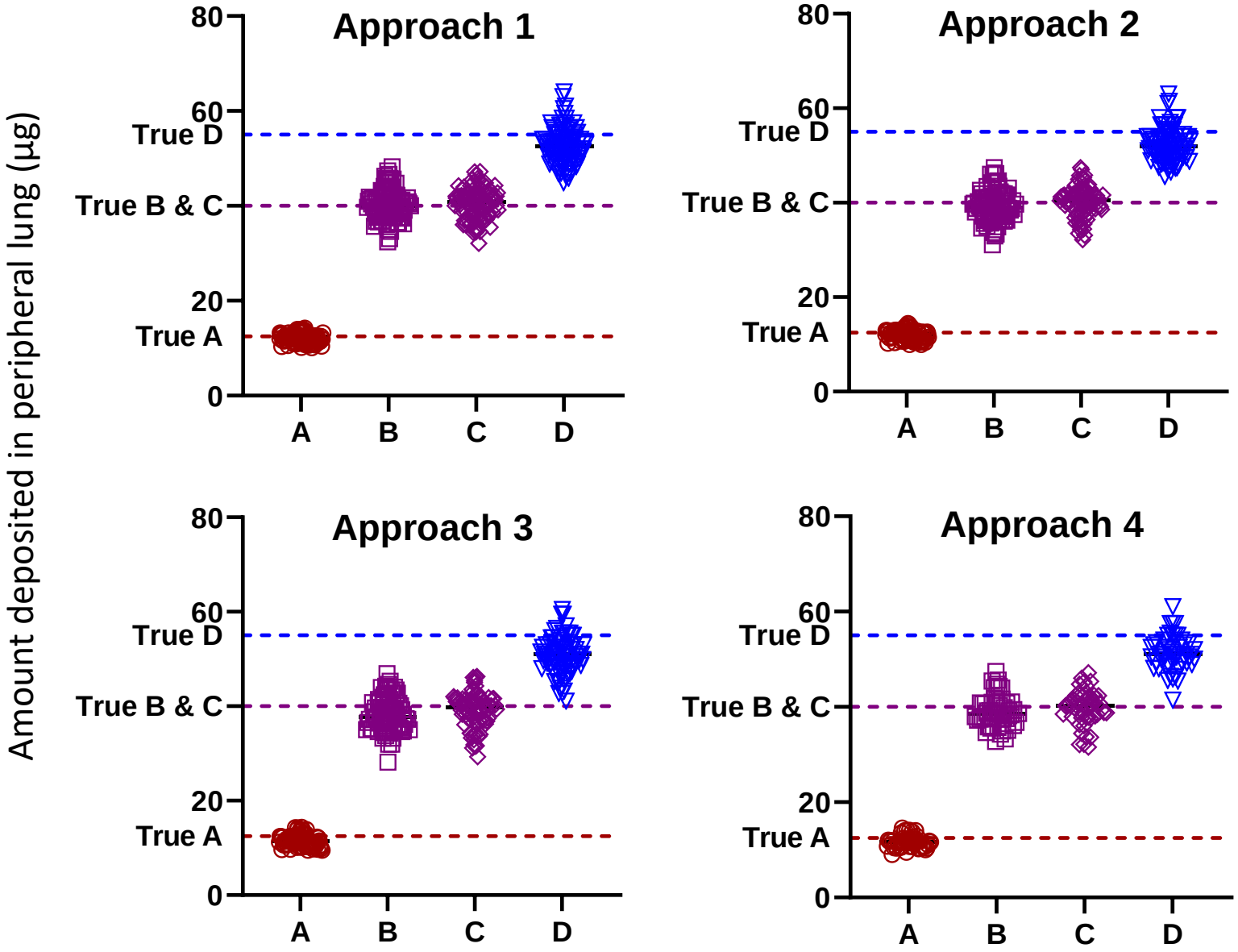
Approach	IV data	Disposition parameters	Comment
1	Individual subject IV data used in estimation	Estimated with reasonable initial estimates (15% off, too small)	**Individual IV PK data in the same subjects**
2	No individual IV data used/available	Population means and BSV fixed to correct values	**Published PopPK parameters** (but no individual subject data; assumed similar subject pop.)
3	No individual IV data used/available	Mean CL fixed, other par. estimated CL's and V's fixed to true values for first 10 iterations subsequently both means and BSV estimated	**Literature PK data** used as **initials only** (careful estimation)
4	No individual IV data used/available	Mean CL fixed, other par. estimated initial estimates 15% off (too small)	**Literature PK data** used as **initials only**

If one considers the modeling of the IV data as the first stage, and modeling of the inhaled data as the 2nd stage, **Approach 1** is similar to a simultaneous fitting of all parameters (**"SIM"** method) and **Approaches 2 to 4** are equivalent to the **"PPP [no IV Data]** method" as defined for sequential popPK/PD analyses by Zhang, Beal & Sheiner JPKPD 2003; 30:387-404).

Amount deposited in peripheral lung

Bias	A	B	C	D
Appr. 1	-2%	0%	2%	-5%
Appr. 2	-2%	-3%	1%	-5%
Appr. 3	-8%	-6%	-1%	-7%
Appr. 4	-7%	-4%	1%	-7%

Precision	A	B	C	D
Appr. 1	8%	8%	8%	7%
Appr. 2	9%	8%	8%	7%
Appr. 3	11%	9%	10%	8%
Appr. 4	11%	8%	9%	7%



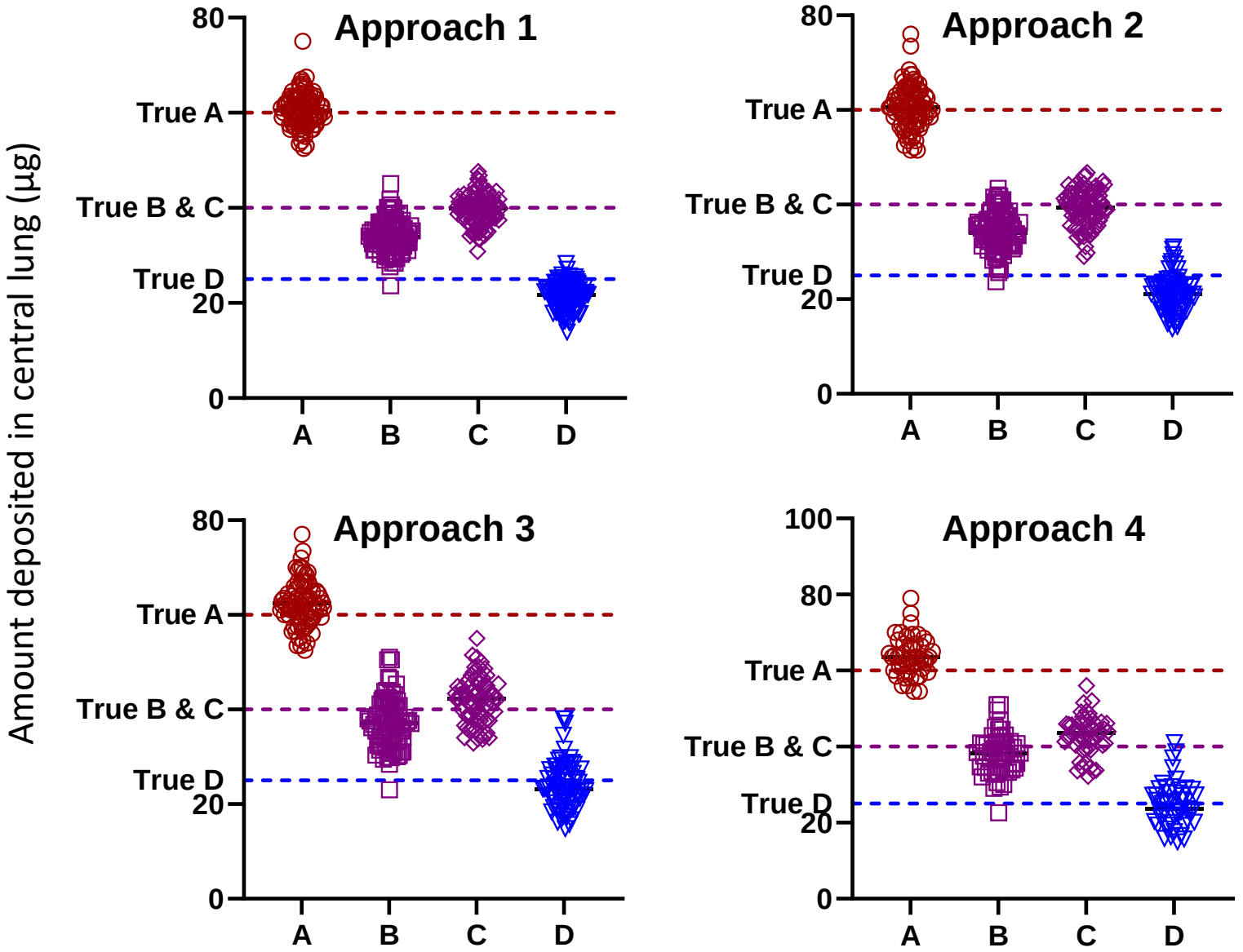
Amount deposited peripherally was best described by approaches 1 and 2.

Amount deposited in central lung

Bias	A	B	C	D
Appr. 1	1%	-15%	0%	-13%
Appr. 2	1%	-15%	-1%	-16%
Appr. 3	4%	-7%	6%	-7%
Appr. 4	6%	-4%	9%	-6%

Precision	A	B	C	D
Appr. 1	6%	10%	8%	13%
Appr. 2	7%	11%	10%	17%
Appr. 3	8%	14%	11%	21%
Appr. 4	8%	15%	12%	23%

The truth is out there …



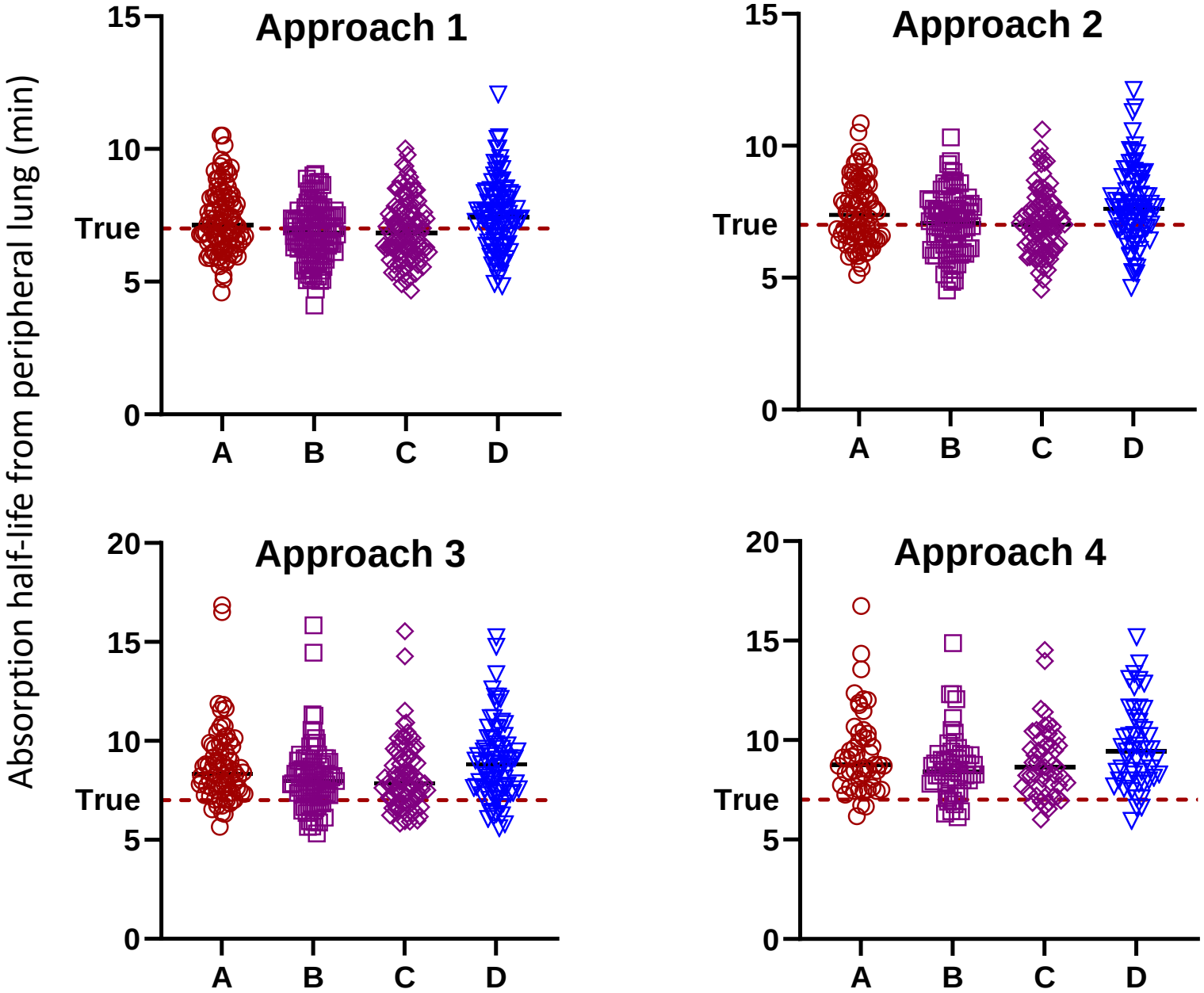
Amount deposited centrally was more difficult to estimate. No approach was statistically significantly biased, but formulations B and D had a downward trend. Approach 1 had the best precision.

Absorption half-life from peripheral lung

Bias	A	B	C	D
Appr. 1	2%	-2%	-2%	6%
Appr. 2	5%	1%	0%	9%
Appr. 3	19%	14%	12%	26%
Appr. 4	25%	20%	23%	35%

Precision	A	B	C	D
Appr. 1	17%	16%	17%	18%
Appr. 2	16%	16%	17%	19%
Appr. 3	22%	21%	21%	22%
Appr. 4	22%	19%	20%	22%

Approach 1 best (with IV PK data).
Approach 2 good at the population level.
Approaches 3 and 4 slightly too high (not significantly though).

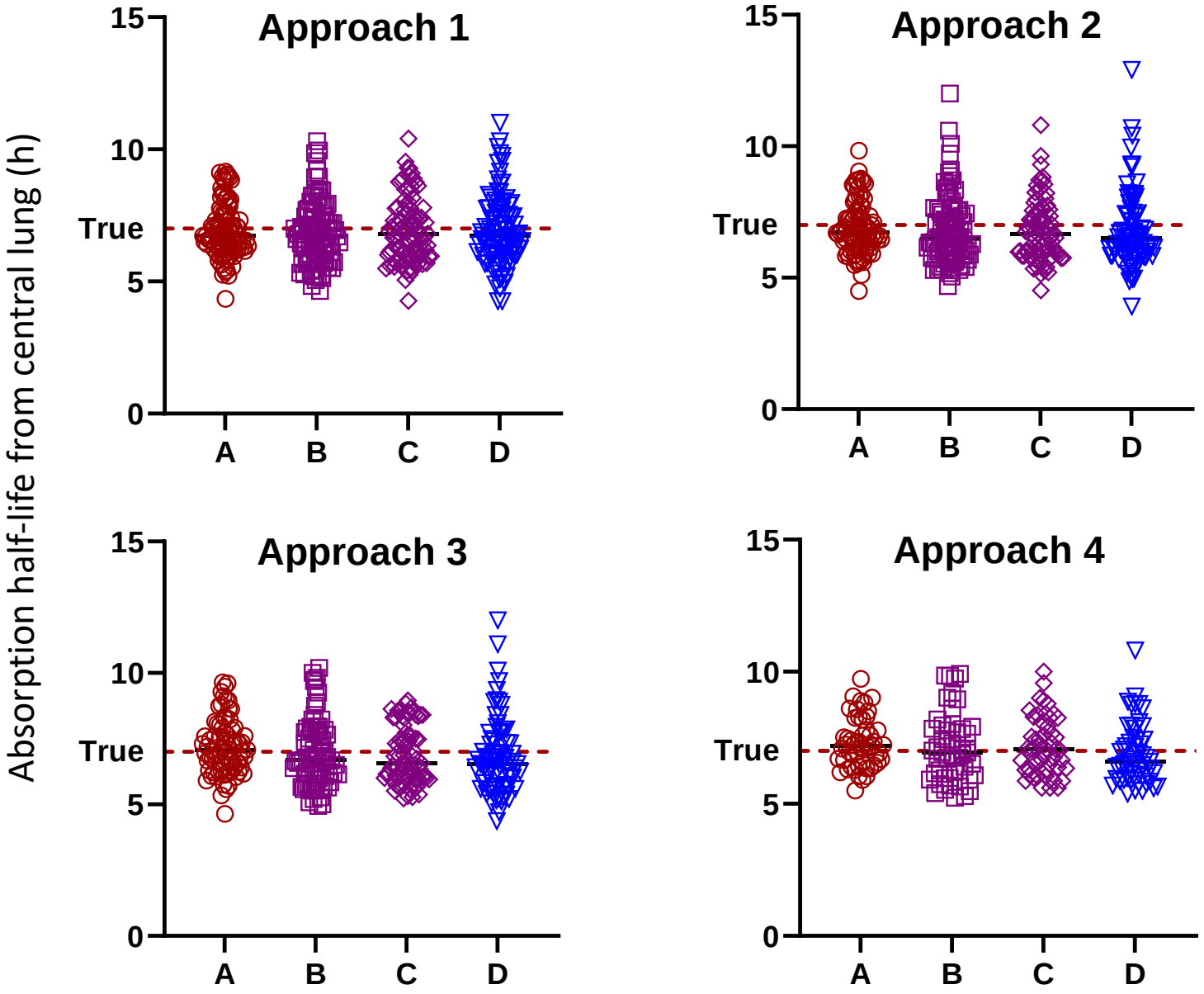


Absorption half-life from central lung

Bias	A	B	C	D
Appr. 1	-4%	-4%	-3%	-4%
Appr. 2	-4%	-7%	-5%	-7%
Appr. 3	1%	-5%	-6%	-7%
Appr. 4	3%	-1%	1%	-6%

Precision	A	B	C	D
Appr. 1	14%	17%	17%	17%
Appr. 2	15%	20%	17%	21%
Appr. 3	15%	18%	15%	21%
Appr. 4	13%	18%	15%	17%

All approaches comparable.



Comparison of individual estimates for first 48 subjects

Ratio of estimated by true individual estimate,

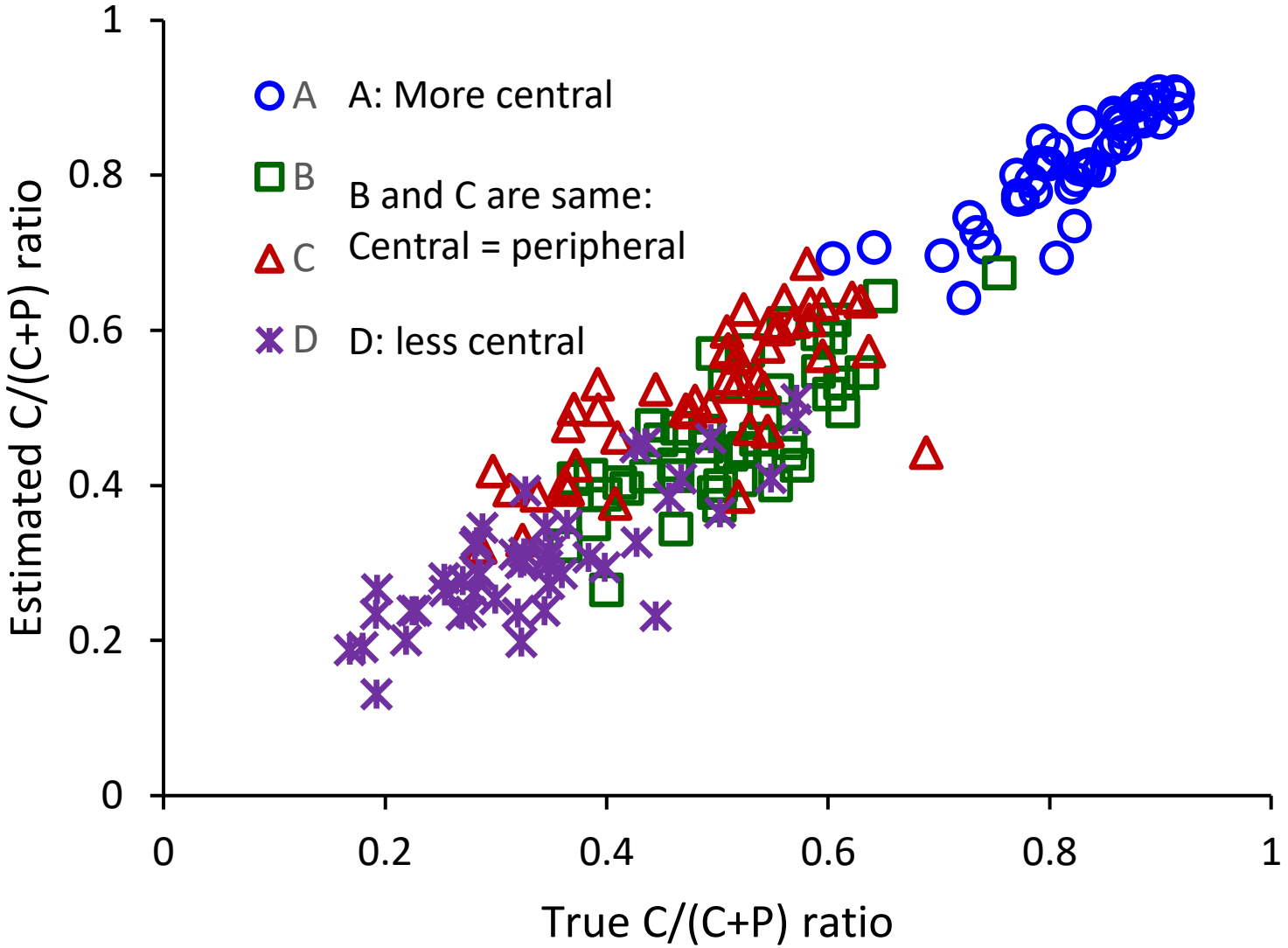
Median (10^{th} – 90^{th} percentile)

	Approach 1	Approach 2	Approach 4
CL	1.01 (0.96 - 1.05)	1.01 (0.94 - 1.14)	1.08 (0.97 - 1.17)
CLD	1.01 (0.74 - 1.28)	1.06 (0.71 - 1.79)	1.02 (0.63 - 1.86)
CLDD	0.99 (0.89 - 1.09)	0.99 (0.91 - 1.13)	1.03 (0.92 - 1.17)
V1	0.96 (0.82 - 1.11)	0.85 (0.63 - 1.34)	0.89 (0.67 - 1.24)
V2	1.05 (0.96 - 1.20)	1.01 (0.90 - 1.15)	0.98 (0.89 - 1.14)
V3	1.02 (0.95 - 1.12)	1.01 (0.86 - 1.12)	1.13 (0.98 - 1.25)

Approach 1 performed best (i.e. simultaneous estimation with individual IV PK data).

Individual subject estimated vs. true C/(C+P)

in 48 subjects x 4 formulations (for approach 1)



r = 0.95

Population PK could clearly distinguish between the four different formulations.

Please note, it is these individual estimates that are used for ANOVA / BE testing.

Conclusions

1. Population PK could distinguish between the **centrally and peripherally deposited** amounts of drug, and inform ANOVA for BE testing in both lung regions.
2. Generating **individual subject IV data** in the same study is recommended. Fixing the disposition parameters to literature estimates performed reasonably.
3. Estimating the model without IV disposition data performed adequately, but tended to be less robust than the above two approaches.
4. Amounts deposited in peripheral and central lung could be robustly estimated. Absorption half-lives were less precise and their between subjects and between occasion variability was large. → NCA Cmax may be more robust to assess absorption rate. → NCA, PopPK, PBPK and other mechanistic approaches are **complementary**.
5. Other drugs / OIDPs would need to be tested to generalize these conclusions beyond fluticasone propionate. Approach likely applicable for other slowly dissolving corticosteroids.
6. **Population PK modeling** could provide valuable insights into the **regional lung deposition** for drugs with bi-phasic absorption that are not accessible by NCA.

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- Views expressed in this presentation do not necessarily reflect the official policies of the U.S. Food and Drug Administration, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.