

# Cystic Fibrosis Patients are Pharmacokinetically Comparable to Healthy Volunteers

J. Bulitta<sup>1</sup>, S. B. Duffull<sup>2</sup>, M. Kinzig-Schippers<sup>1</sup>,  
U. Holzgrabe<sup>3</sup>, U. Stephan<sup>1,4</sup>, F. Sörgel<sup>1,4</sup>

1: IBMP, Nürnberg, Germany

2: University of Queensland, Australia

3: University of Würzburg, Germany

4: University of Duisburg – Essen, Germany

# Objectives

- 1) To compare average clearance (CL) and volume of distribution (Vd) between cystic fibrosis (CF) patients and healthy volunteers.  
→ “Does CF alter pharmacokinetics?”
- 2) To study which body size descriptor reduces the unexplained between subject variability in CL and Vd most.  
→ “How to achieve target concentrations more precisely?”

# Literature data<sup>1</sup>

studies with CF-patients and healthy volunteers (H)

Range for the	Ratio of average clearance $CL(CF) / CL(H)^*$	Ratio of average volume of distribution $Vd(CF) / Vd(H)^{**}$
Penicillins	1.17 – 2.54	1.16 – 1.41
Cephalosporins	0.95 – 1.65	0.64 – 1.44
Aminoglycosides	0.83 – 1.88	0.86 – 1.42
Ciprofloxacin	0.90 – 1.46	0.56 – 1.62

\*Clearance expressed as L/h/kg total body weight (or as L/h/m<sup>2</sup> BSA).

\*\*Volume of distribution expressed as L/kg total body weight (or L/m<sup>2</sup>).

<sup>1</sup>Touw DJ et al., Clin Pharmacokinet 1998, 35:437-59.

# Clinical studies

- 10\* antibiotics (7 beta-lactams, 3 quinolones)
- Similar clinical protocols
- All studies with a healthy volunteer control group
- Frequent plasma and urine samples
- Similar clinical study conditions for CF-patients and healthy volunteers
- Validated HPLC analysis in a single laboratory

\*: Carumonam, cefaclor, cefadroxil, cefotiam, ceftazidime, cefpirome, ciprofloxacin, fleroxacin, pefloxacin, piperacillin

# Demographics

	CF- patients	Healthy volunteers	Ratio CF / H
Number of subjects	90	111	
Age (yr)	21 ± 3.6	25 ± 3.5	84%
Height (cm)	167 ± 11	174 ± 8.3	96%
Total body weight (kg)	50 ± 11	68 ± 11	<b>73%</b>
Lean body mass (kg)*	42 ± 8.6	54 ± 7.9	<b>78%</b>
Body mass index (kg m <sup>-2</sup> )	18 ± 2.7	23 ± 2.9	79%

\*Cheymol & James formula

# Pharmacokinetic analysis

- Population PK with NONMEM® V  
(FOCE with interaction)
- 2-compartment models
- Exponential between subject variability model
- Model qualification via visual predictive checks
- Non-parametric bootstrap for point estimates  
(medians) & confidence intervals (Perl / NONMEM®)
- Statistics and non-compartmental analysis with  
WinNonlin®

# Size models

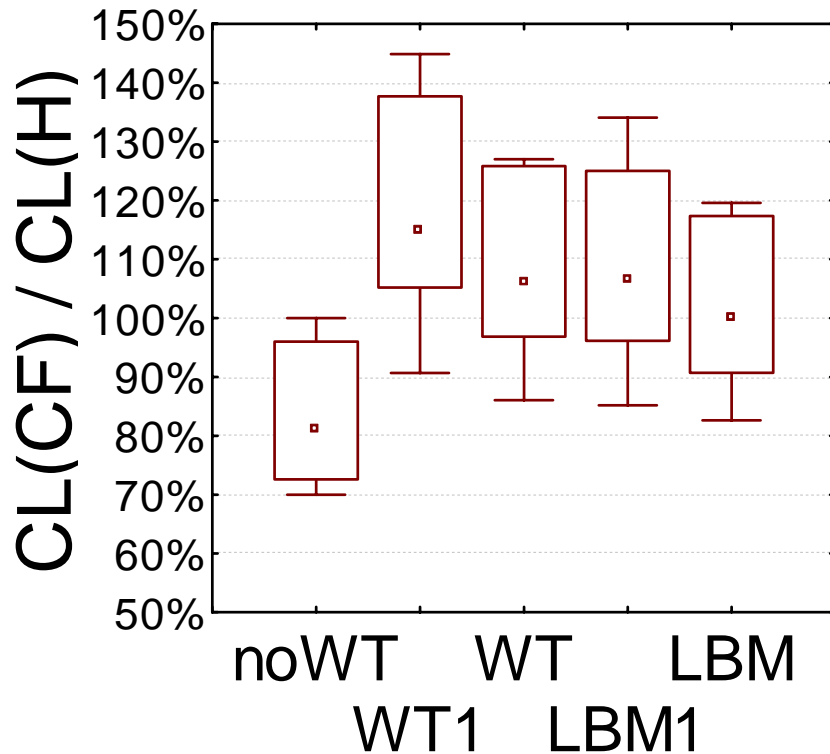
Size model	Name	Exponent for	
		CL	Vd
1) No size model	noWT		
<i>Total body weight</i>			
2) Linear scaling	WT1	1.0*	1.0
3) Allometric scaling	WT	0.75**	1.0
<i>Lean body mass</i>			
4) Linear scaling	LBM1	1.0*	1.0
5) Allometric scaling	LBM	0.75**	1.0

\*: “Double the size, double the clearance.”

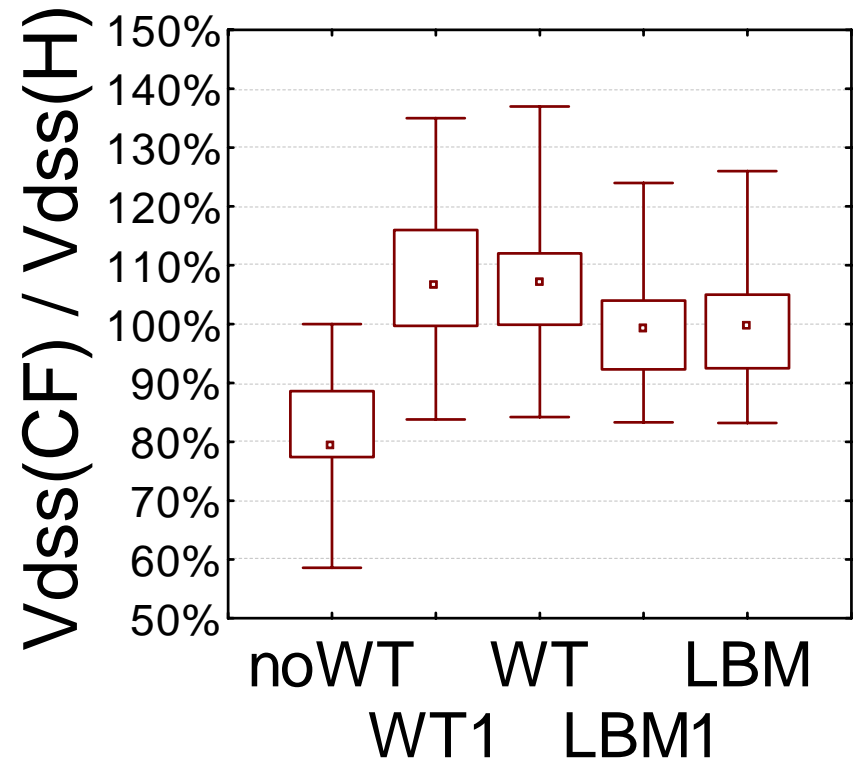
\*\* : “Double the size, increase clearance by 68%.”

# Average ratios for 10 antibiotics after size adjustment

## Total clearance (CL)



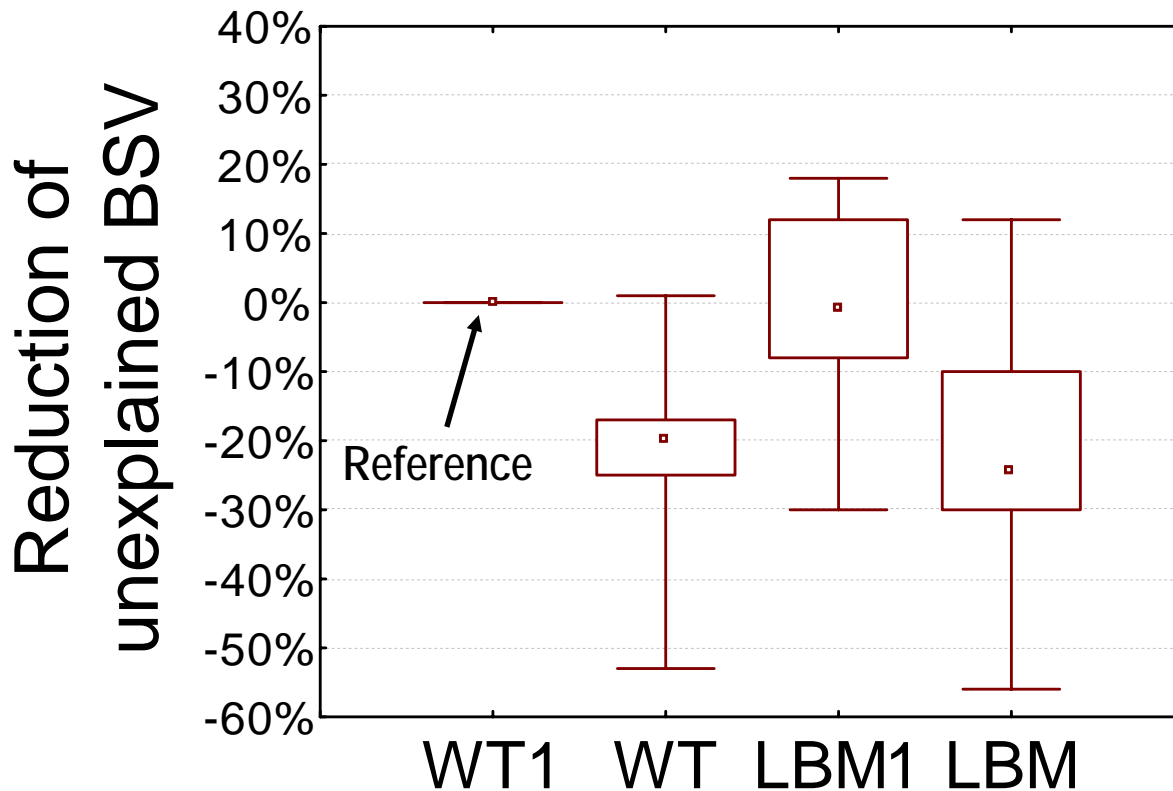
## Volume of distribution at steady-state (Vdss)



**Marker:** Median of 10 drugs, **Box:** inter-quartile range, **Whisker:** Min-Max

# Reduction of unexplained between subject variability (BSV)

## Renal clearance

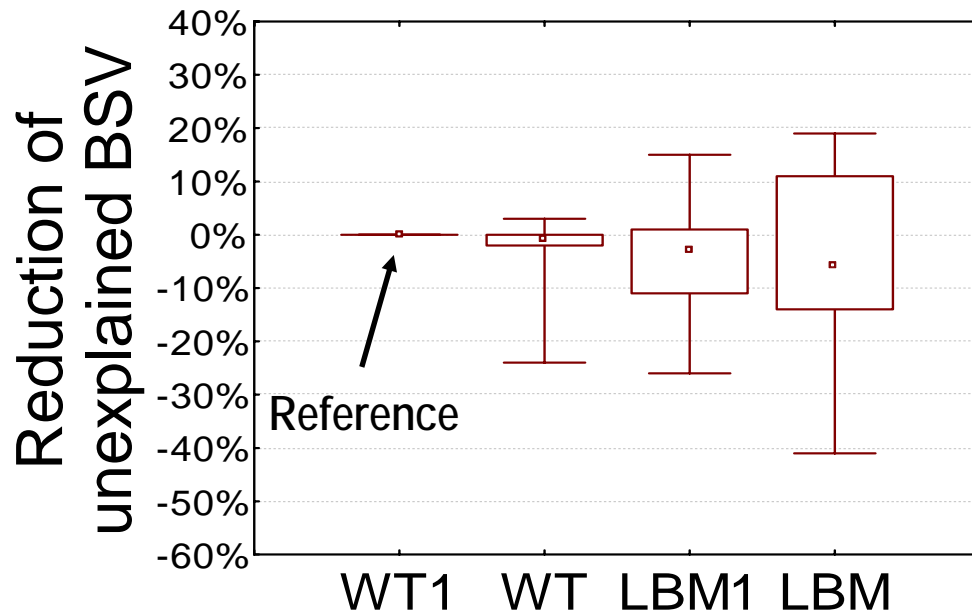


→ Reduction of BSV by **20-25%** after adjusting for the average difference in renal clearance between both subject groups

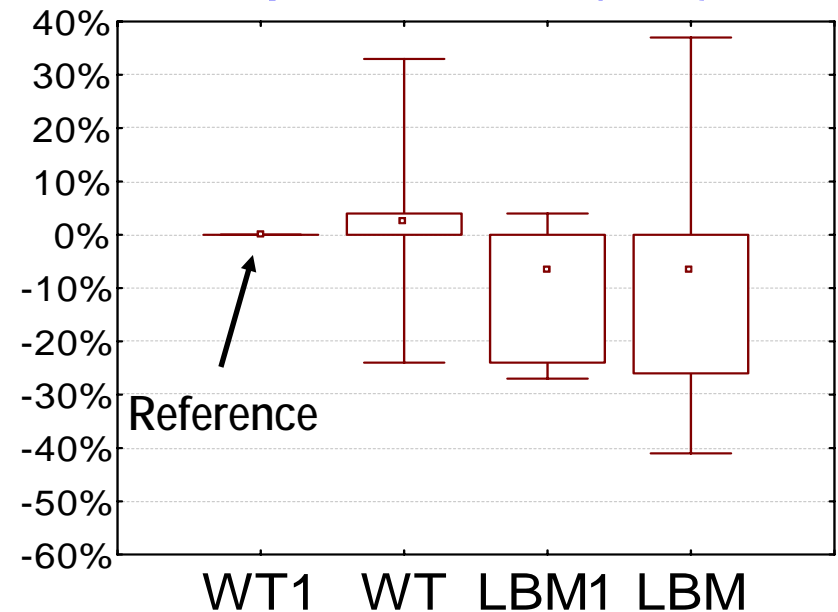
**Marker:** Median of 10 drugs, **Box:** inter-quartile range, **Whisker:** Min-Max

# Reduction of unexplained between subject variability (BSV)

## Volume of central compartment (V1)



## Volume of peripheral compartment (V2)



→ None of the comparisons were statistically significant.

**Marker:** Median of 10 drugs, **Box:** inter-quartile range, **Whisker:** Min-Max

# Conclusions

## Allometric scaling by LBM:

- explained the difference in average CL and Vd between adult CF-patients and healthy volunteers
- reduced the unexplained BSV in renal clearance **by 25%** relative to linear scaling by WT
- allows one to
  - predict individual renal clearance more precisely
  - achieve target concentrations more precisely in adult CF-patients

# Acknowledgement

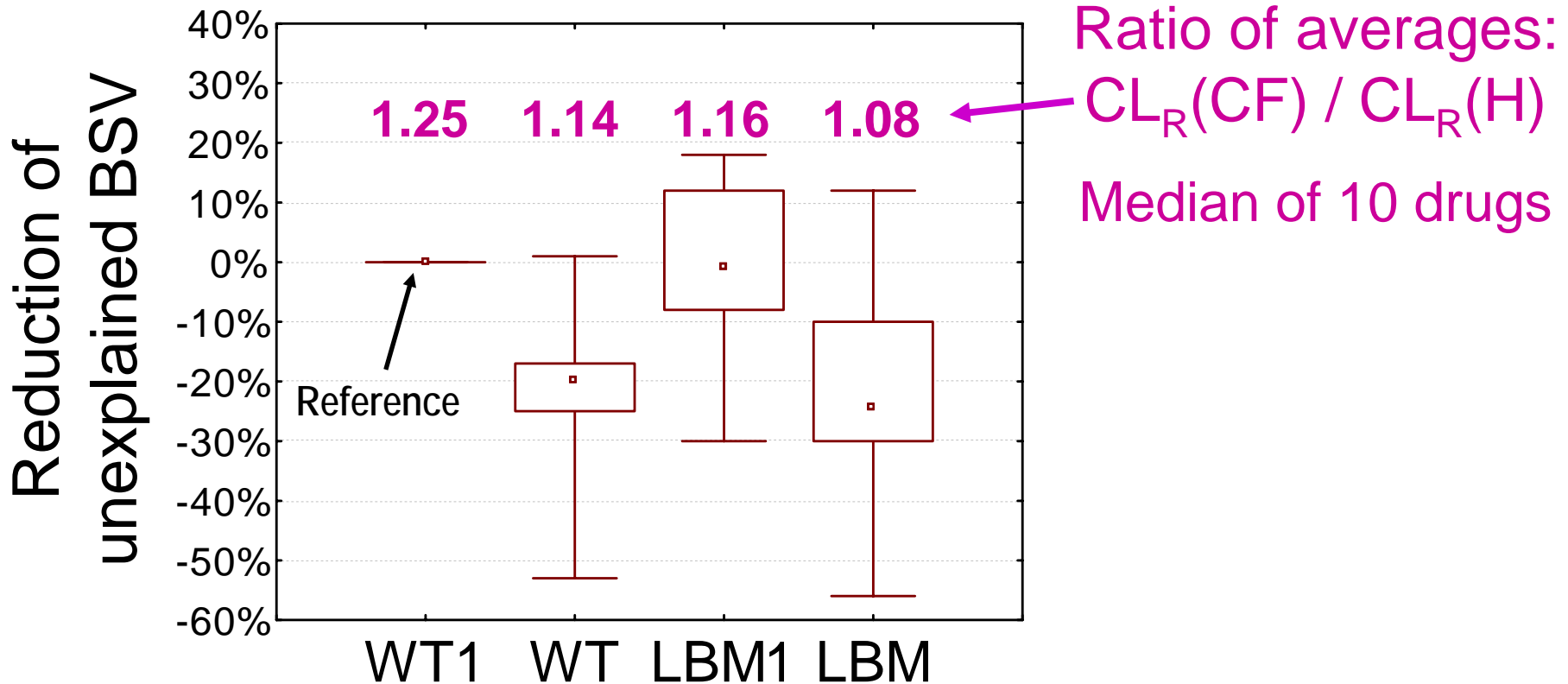
My warmest thank you to:

- All Clinical Study Teams
- All people in the bio-analytical lab
- Ms. Cornelia Landersdorfer
- Dr. Nick H. G. Holford
- Dr. George L. Drusano

Thank you very much  
for your attention.

# Reduction of unexplained between subject variability (BSV)

## Renal clearance

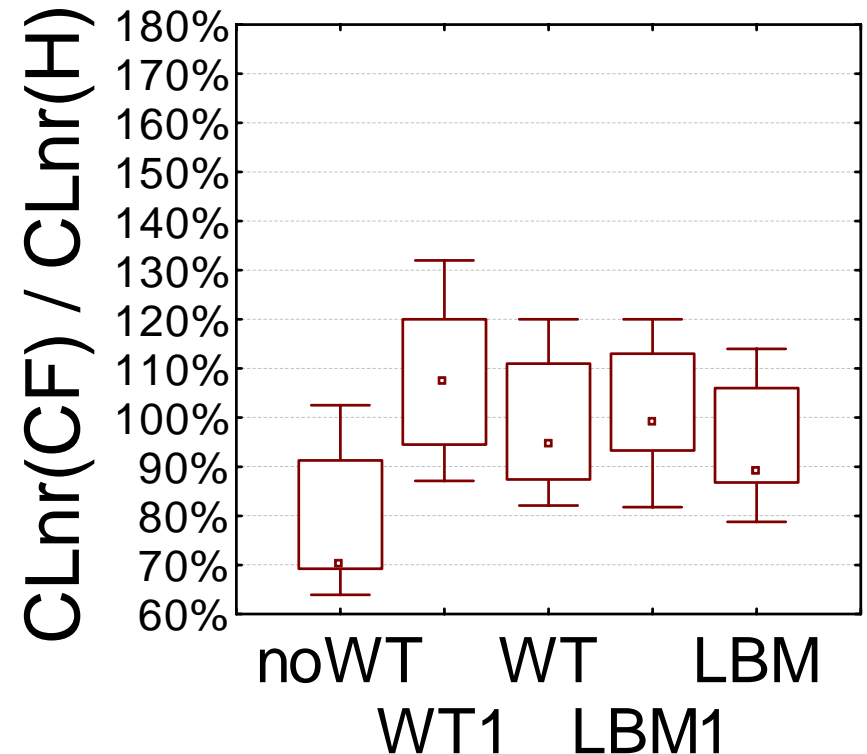
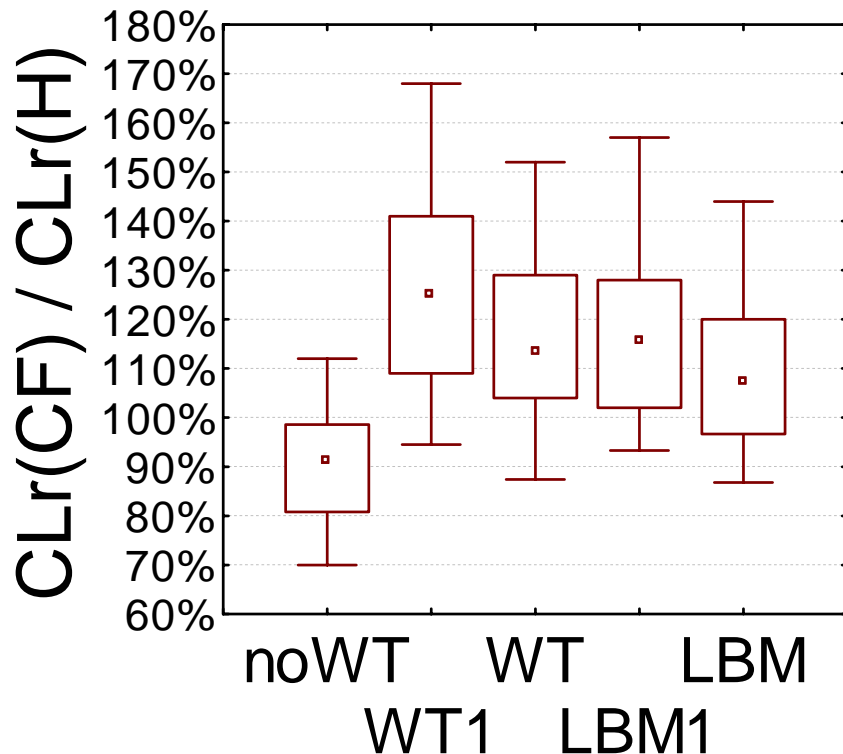


**Marker:** Median of 10 drugs, **Box:** inter-quartile range, **Whisker:** Min-Max

# Average ratios after size adjustment

Renal clearance (CLr)

Non-renal clearance (CLnr)



**Marker:** Median of 10 drugs, **Box:** inter-quartile range, **Whisker:** Min-Max