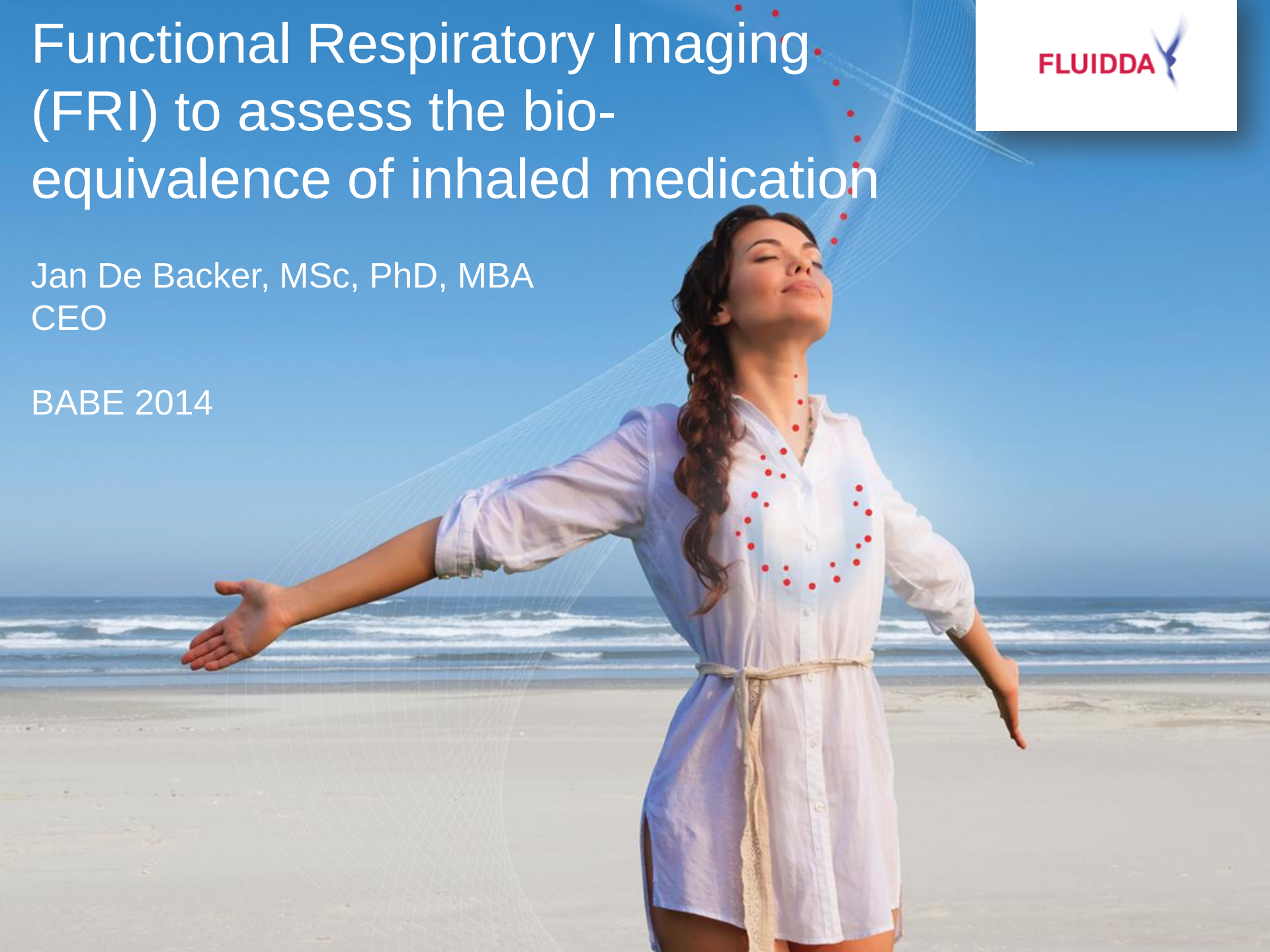
Functional Respiratory Imaging (FRI) to assess the bio-equivalence of inhaled medication

Jan De Backer, MSc, PhD, MBA
CEO

BABE 2014



FLUIDDA

OVERVIEW

- **Functional Respiratory Imaging (FRI)**
  - FRI outcome parameters
  - Added value in drug and device development
- **Bio-equivalence**
  - Salmeterol/Fluticasone branded vs generic in asthma
  - Salbutamol vs Ipratropium Bromide in COPD
- **Conclusions**

CHALLENGES IN RESPIRATORY DRUG DEVELOPMENT

Limited sensitivity of current Pulmonary Function Tests (FEV1,…)

Very difficult to demonstrate efficacy of novel compounds, resulting in **high number of patients needed in clinical trials**

Excessive respiratory drug development cost > $1.5 billion

Difficult to demonstrate bio-equivalence

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AIM

- Explain Functional Respiratory Imaging (FRI)
- Demonstrate enhanced sensitivity wrt PFT
- Reduction in # patients required for clinical trials to understand mode of action
- Use clinical trials as a design tool in phase I and II
  - To assess bioequivalence
  - To de-risk phase III

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IMAGING BIOMARKERS

- FRI is an imaging biomarkers for respiratory diseases
  - What are imaging biomarkers?

According to Wikipedia:

"A biomarker, or biological marker, generally refers to a **measured** characteristic which may be used as an indicator of some **biological** state or condition."

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IMAGING BIOMARKERS

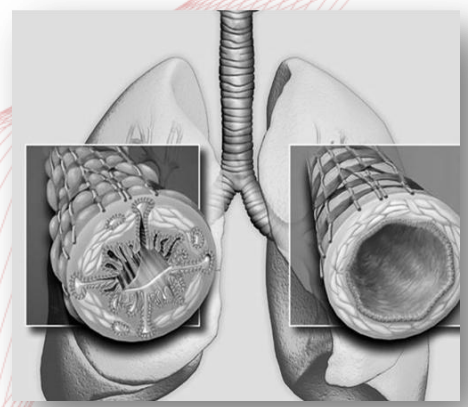
Event

Biomarker

Intervention

FLUIDDA

IMAGING BIOMARKERS

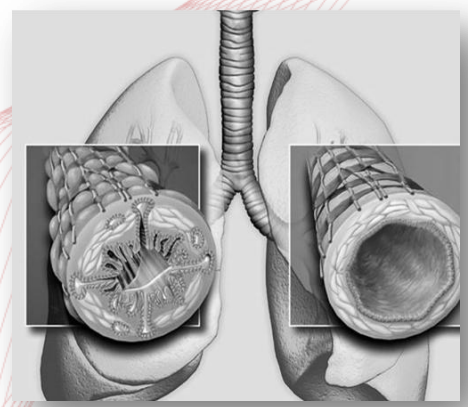


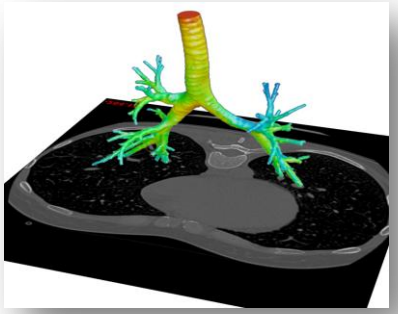
Event

Biomarker

Intervention

IMAGING BIOMARKERS





Event

Biomarker

Intervention

FLUIDDA FUNCTIONAL RESPIRATORY IMAGING

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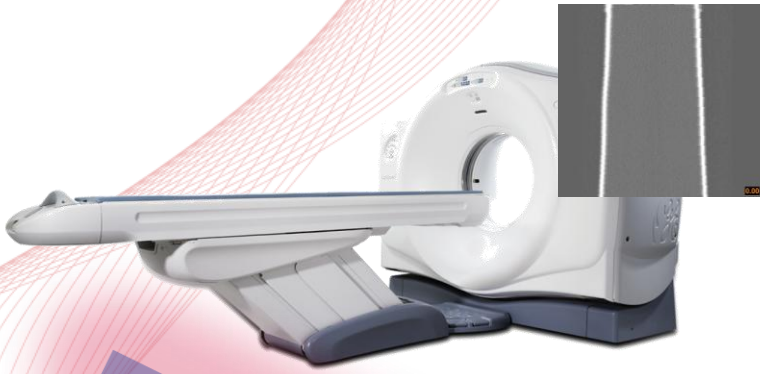
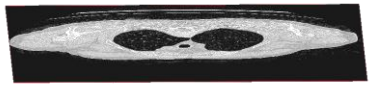
FUNCTIONAL RESPIRATORY IMAGING (FRI)



scan



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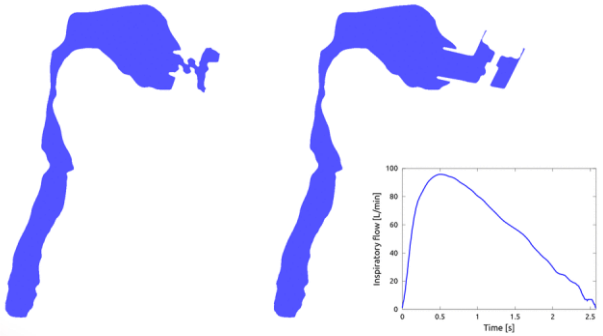

simulate flow

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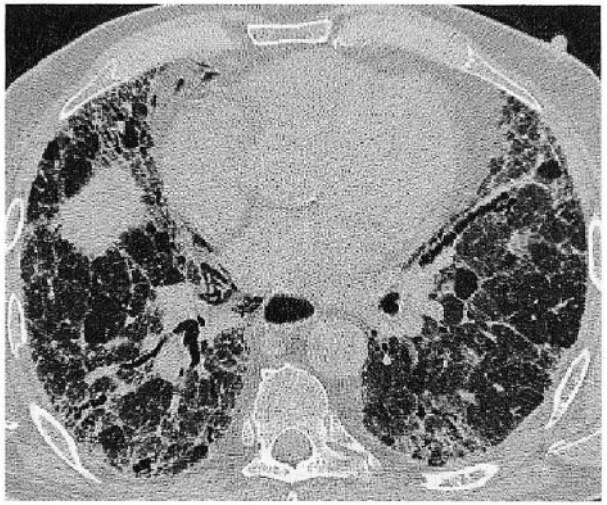
FUNCTIONAL RESPIRATORY IMAGING (FRI)

- High-resolution CT images are converted into patient-specific 3D computer models



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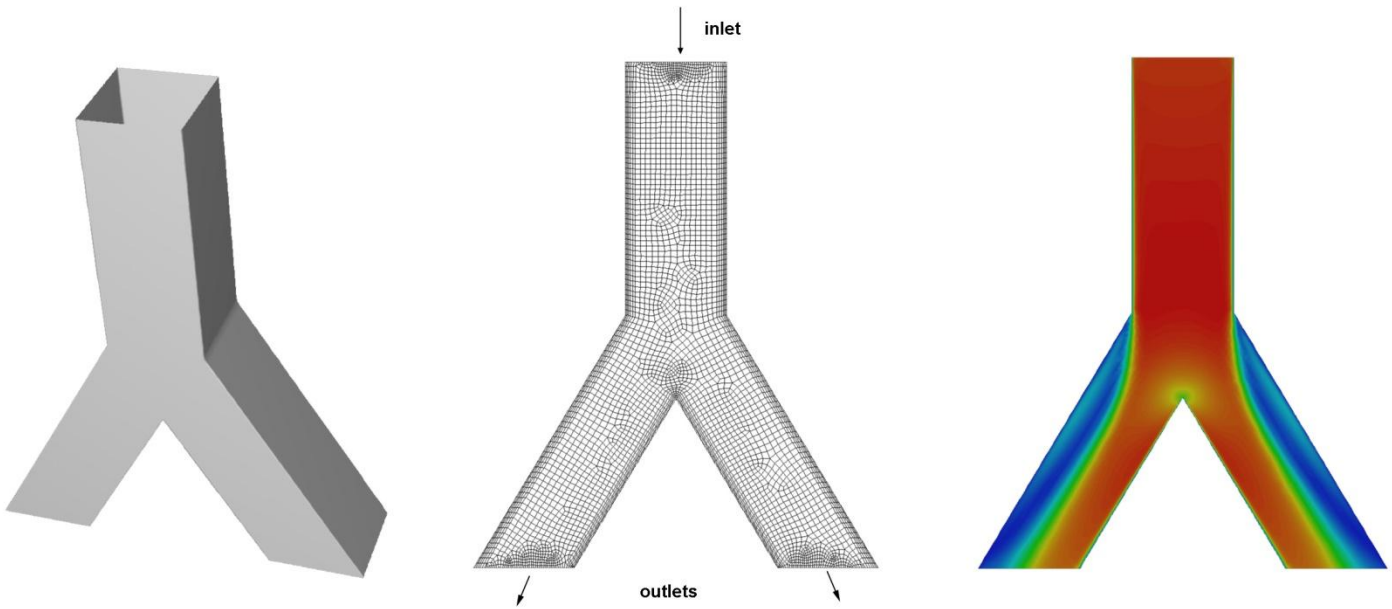
FUNCTIONAL RESPIRATORY IMAGING (FRI)

- Computational Fluid Dynamics
- Solving Navier-Stokes equations numerically
- Computational grid
- Boundary conditions



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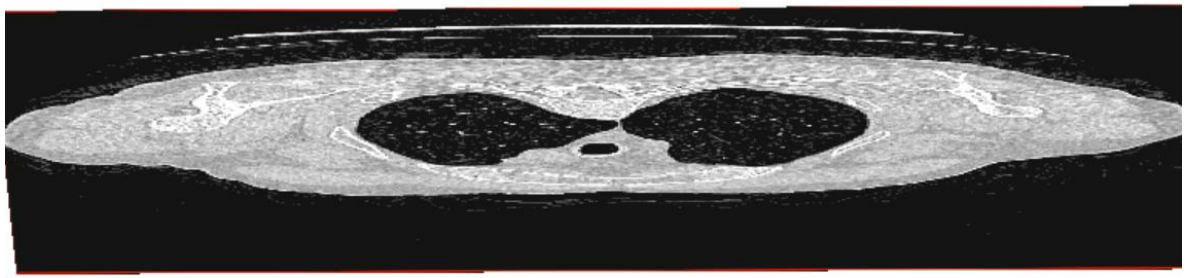
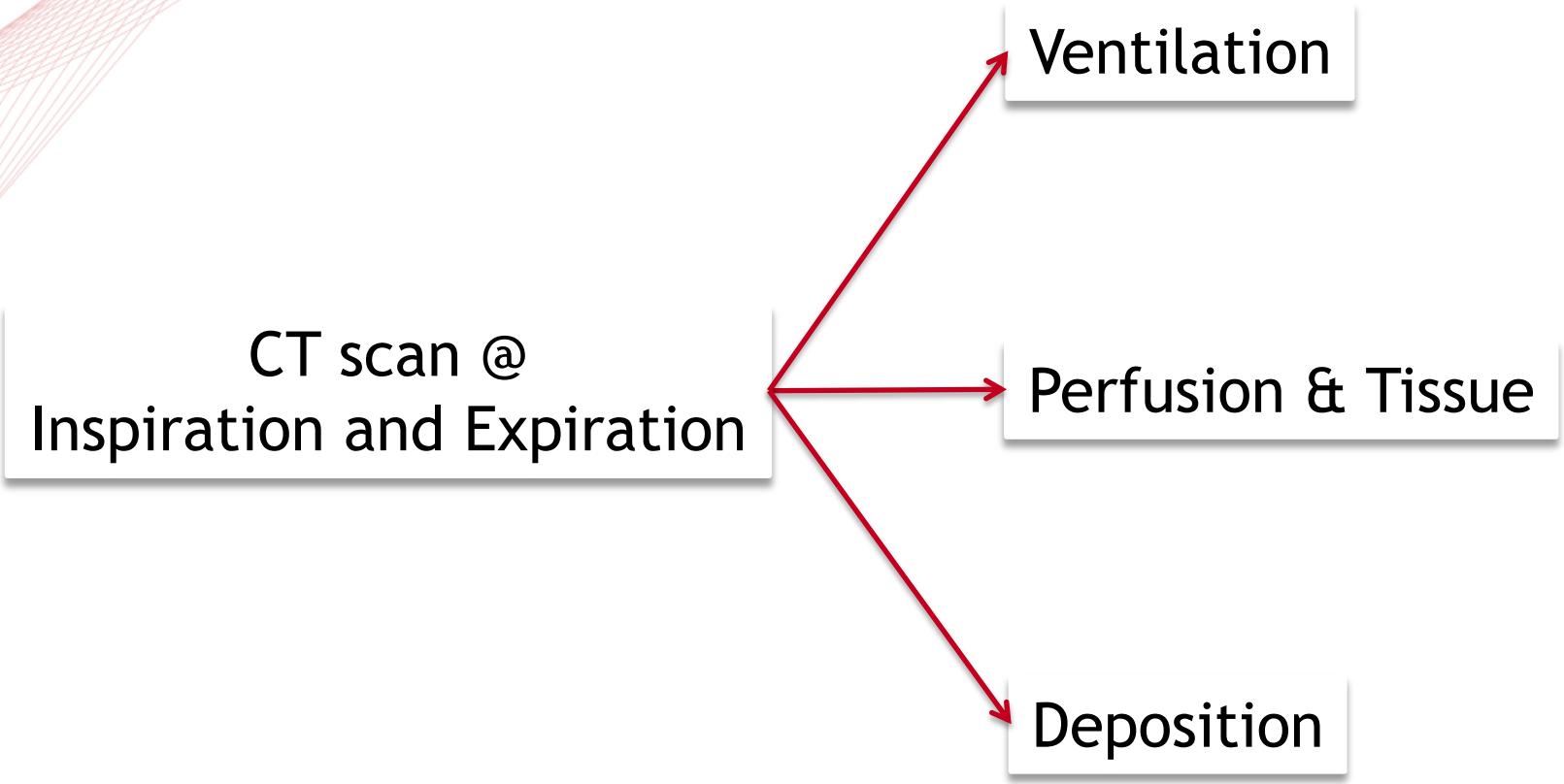


FRI OUTCOME PARAMETERS



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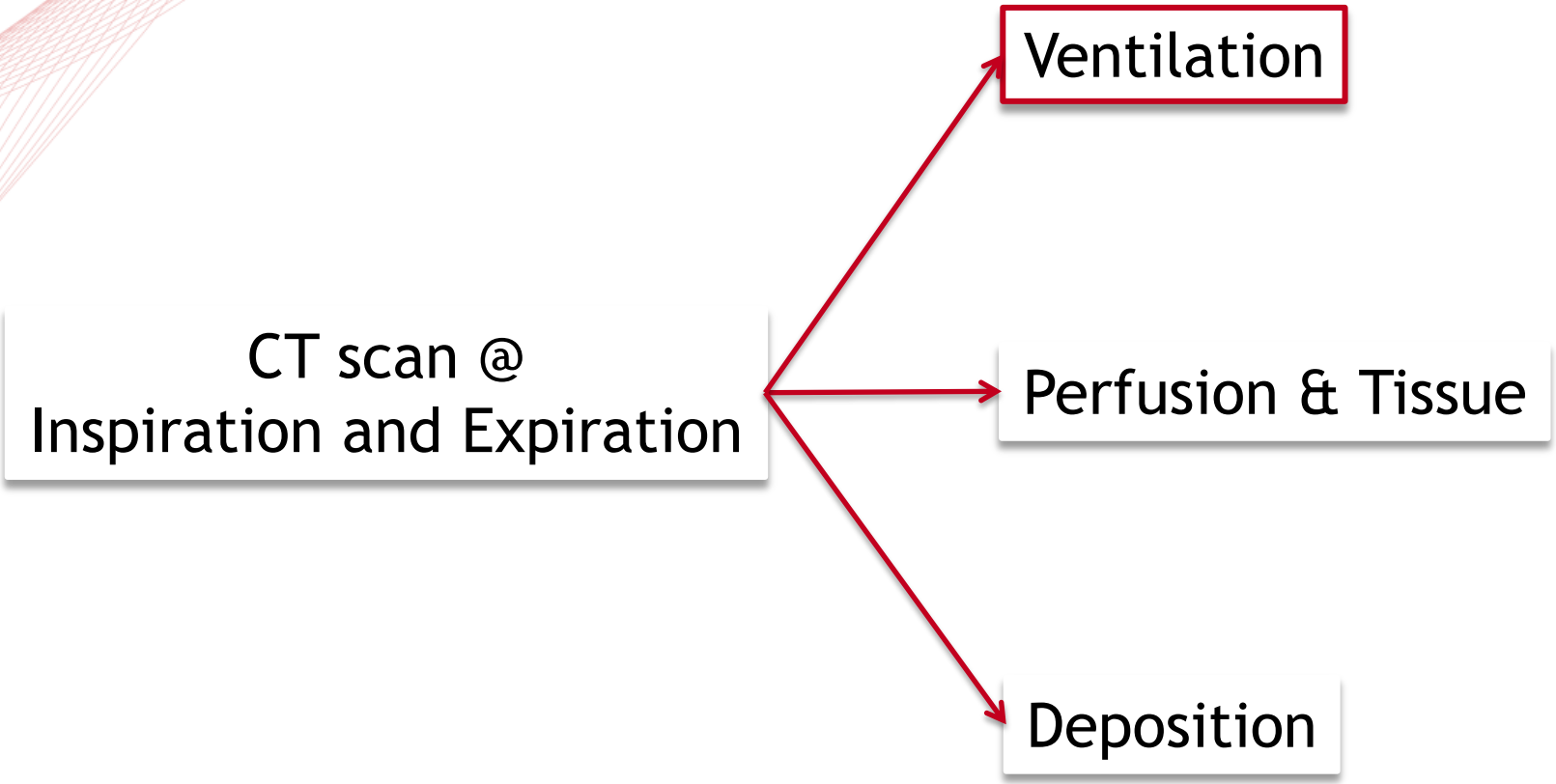

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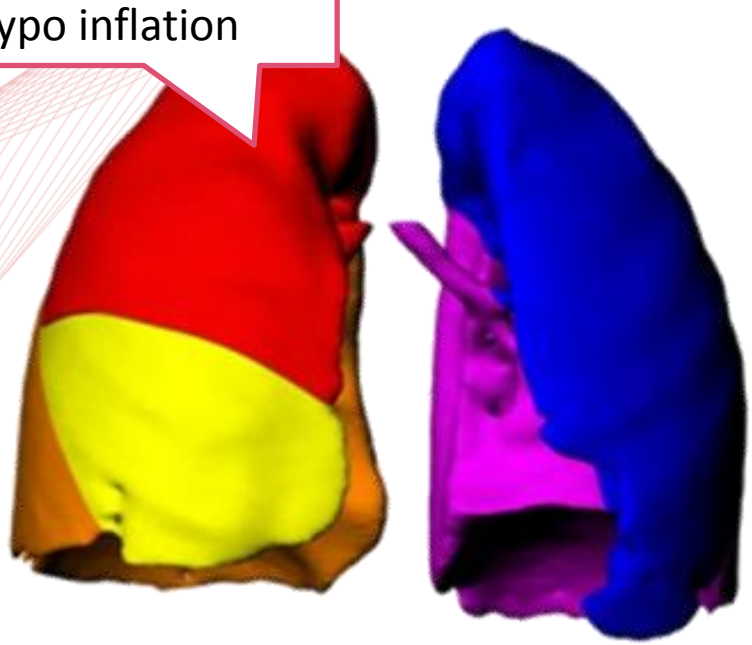
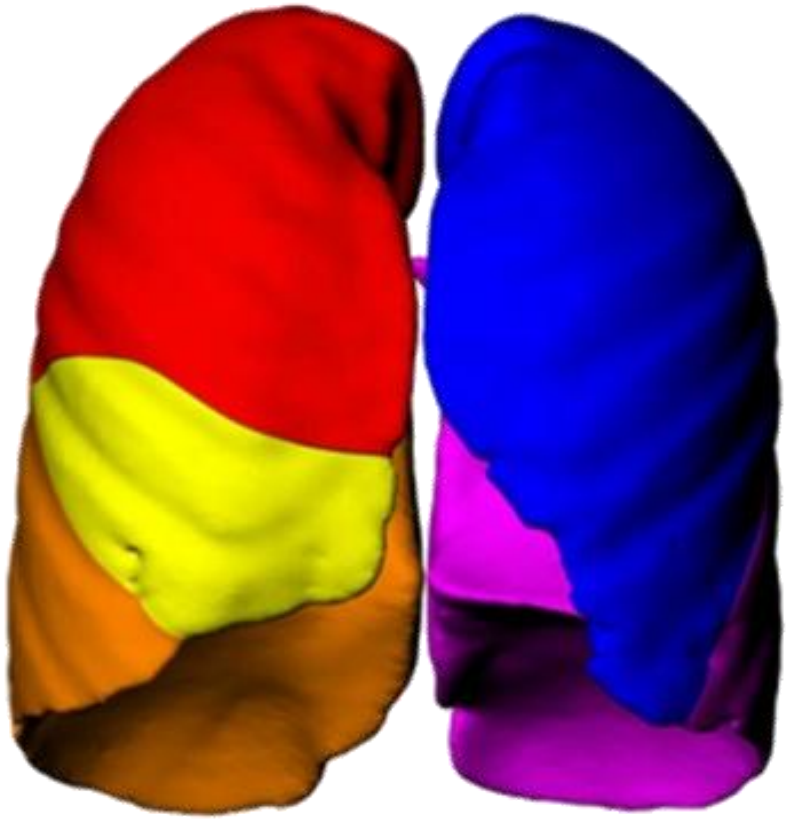
FRI: VENTILATION

Lobar Volumes

Lobe volumes could be expressed as %p to assess hyper- or hypo inflation



FRC

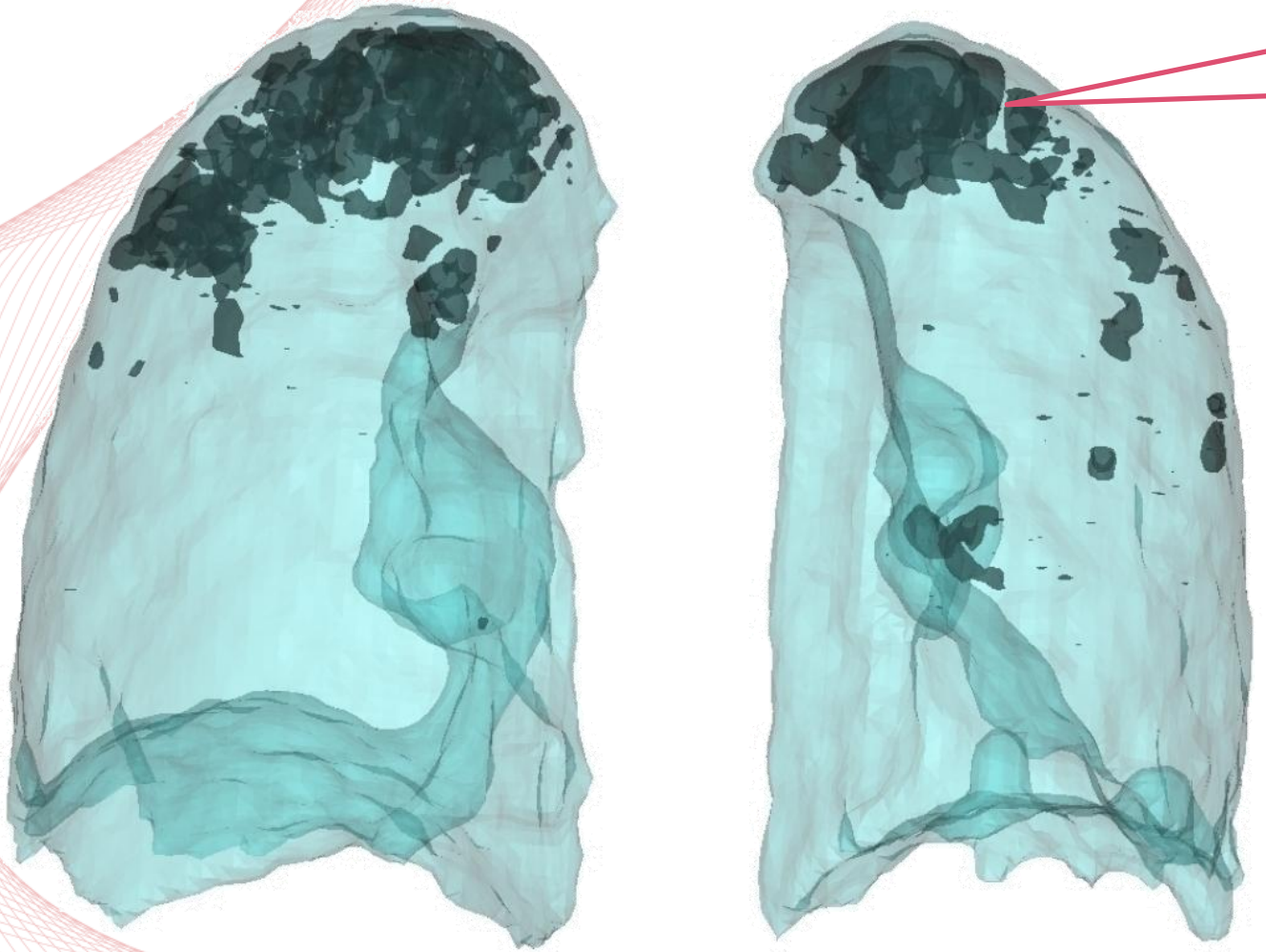


TLC

Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

FRI: VENTILATION

Air Trapping



Fraction of volume with HU <-850 on FRC scan

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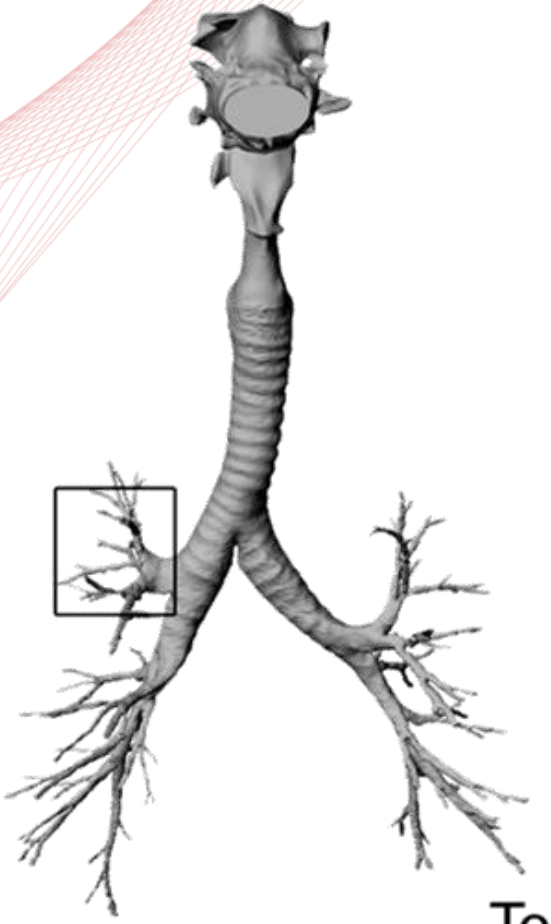
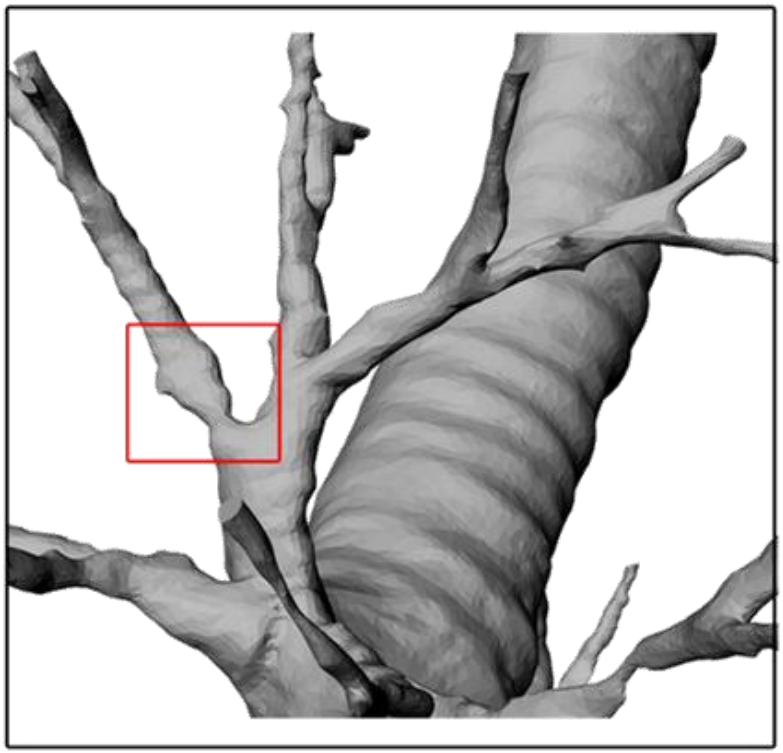
FRI: VENTILATION

Airway Volumes





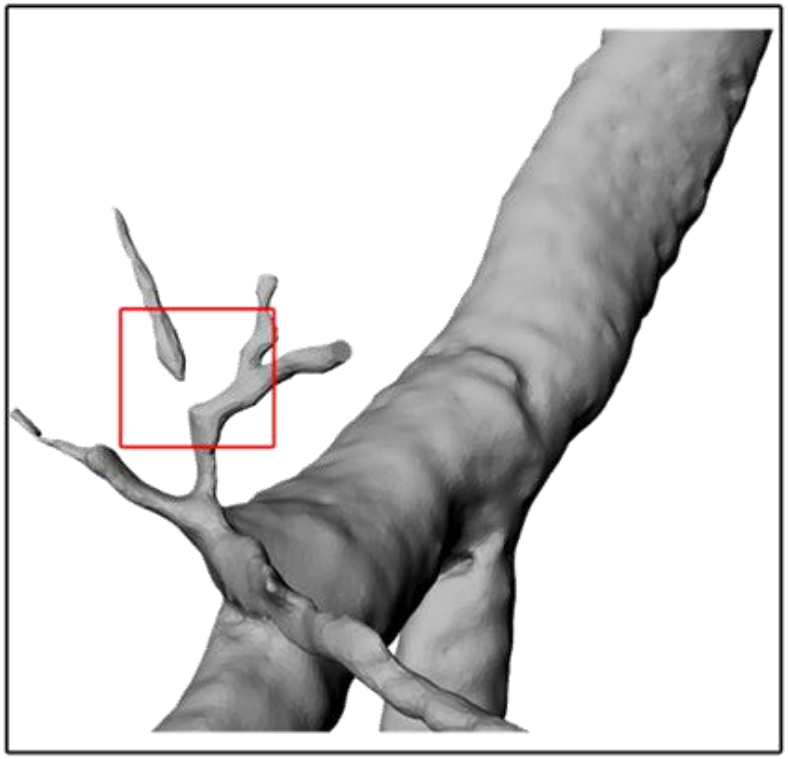
Total Lung Capacity

Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

FLUIDDA

FRI: VENTILATION

Airway Volumes



Functional Residual Capacity

Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

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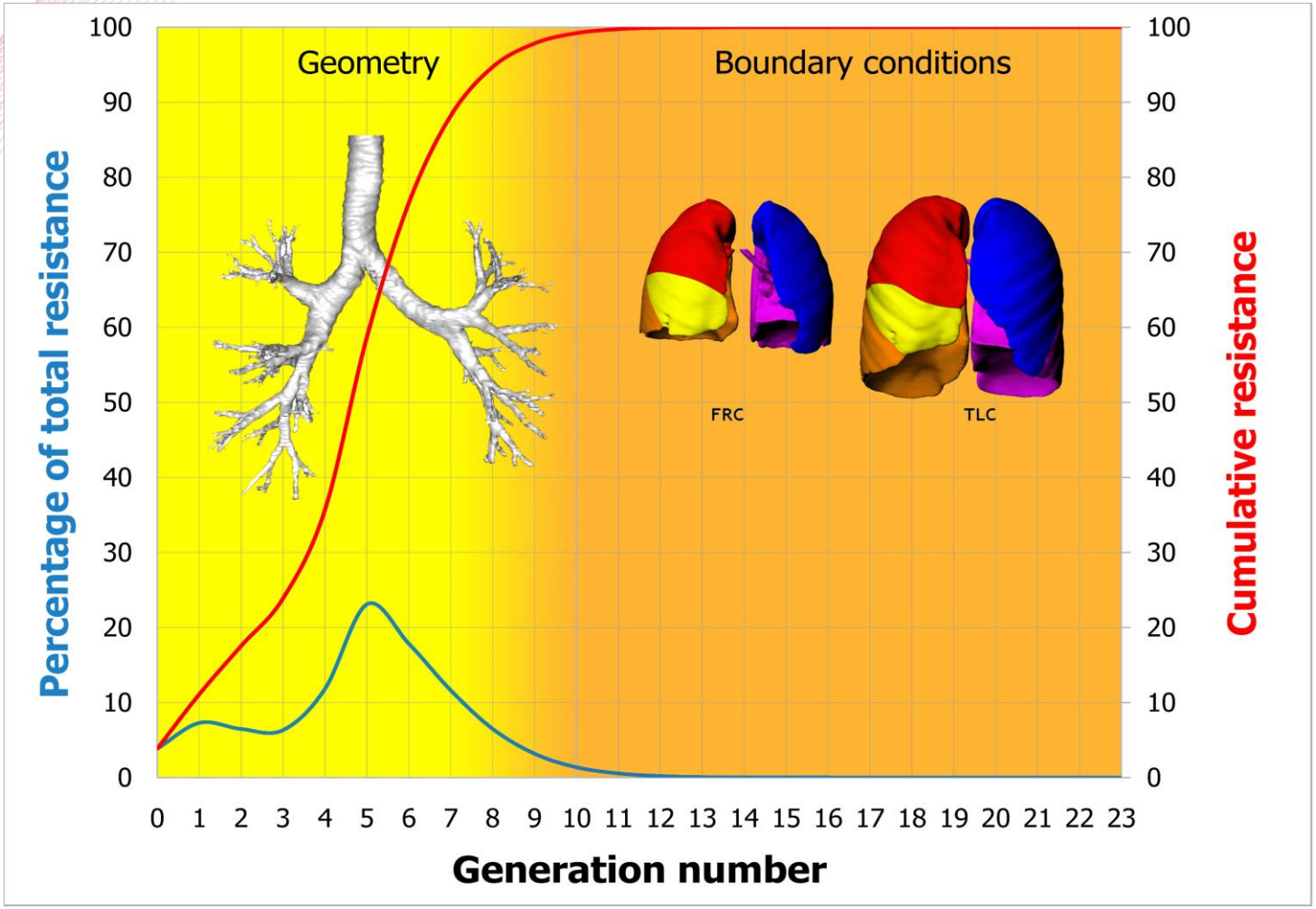
FRI: VENTILATION

Airway Resistance



Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

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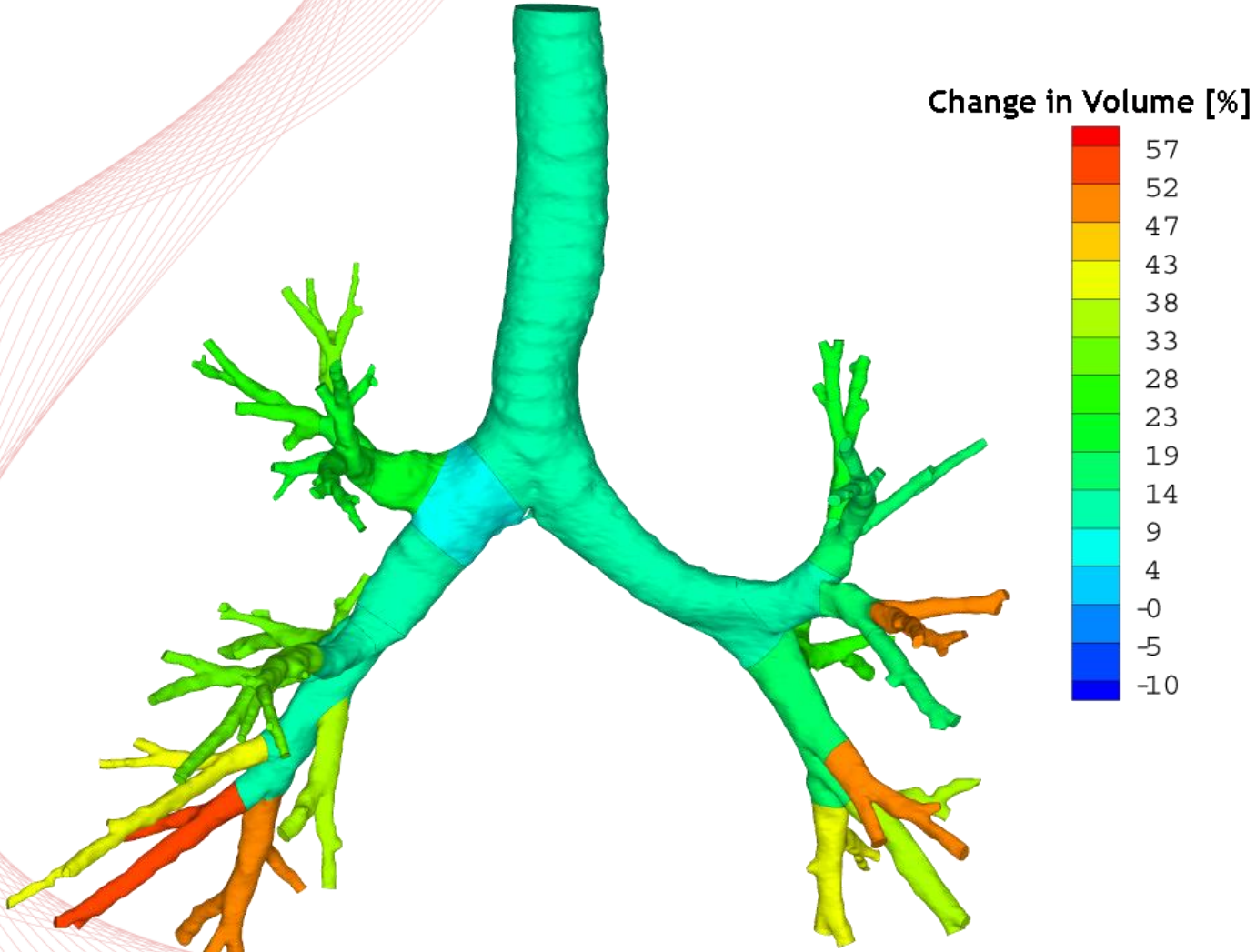
FRI: VENTILATION

Image-based airway volume (iVaw) change

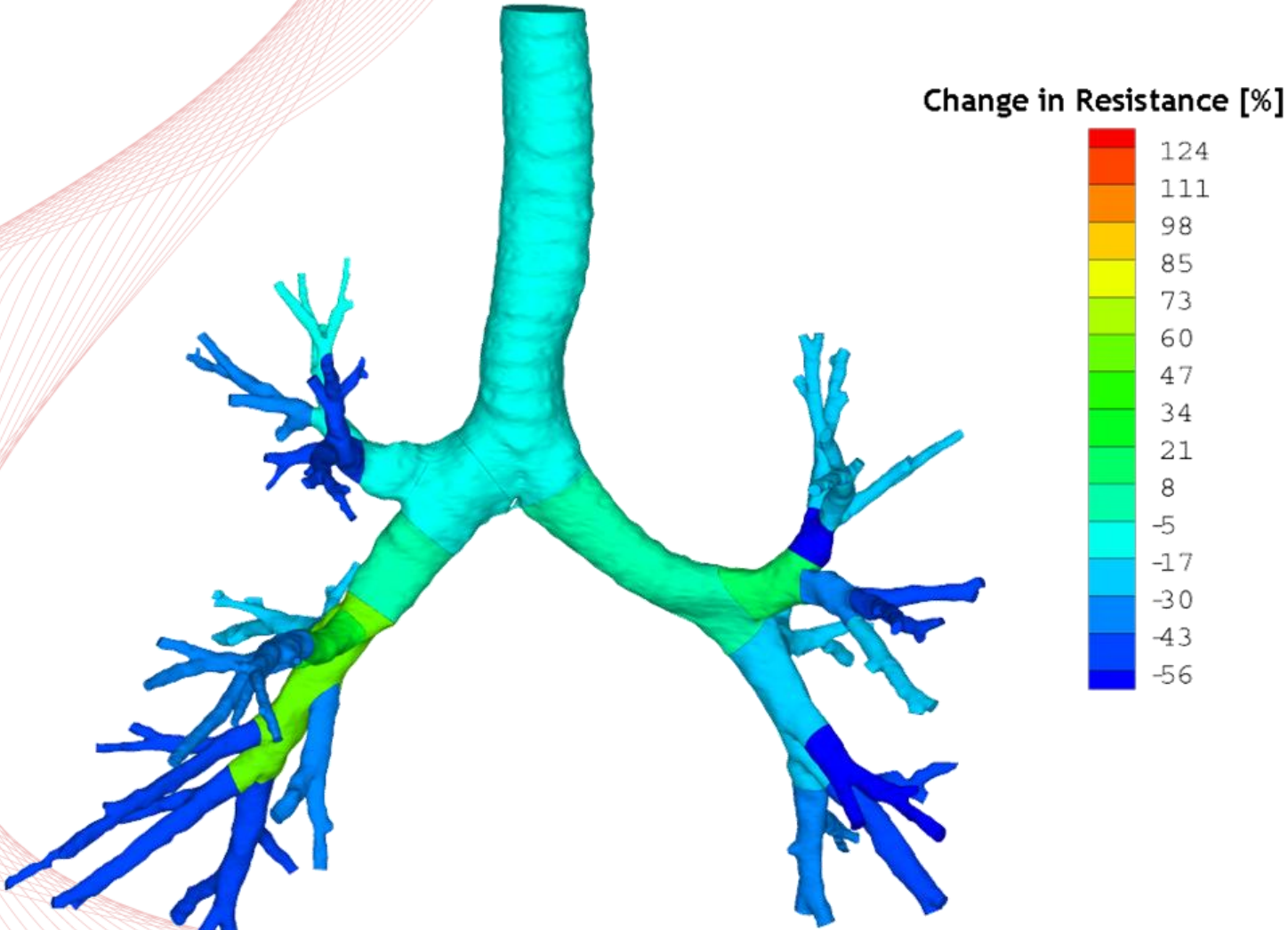


Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

FLUIDDA

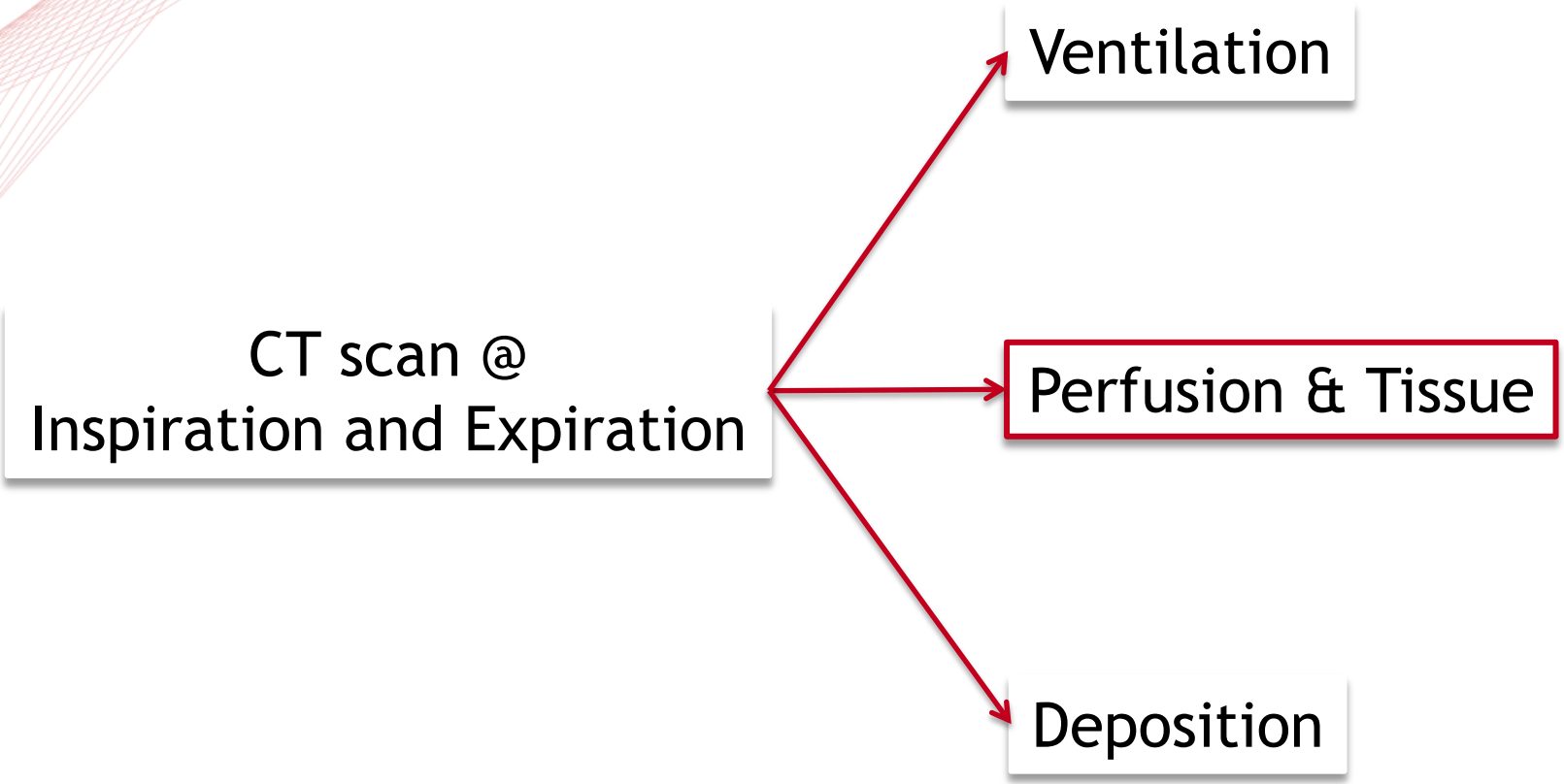
FRI: VENTILATION

CFD-based airway resistance (iRaw) change



Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

FRI OUTCOME PARAMETERS



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FRI: PERFUSION

Emphysema

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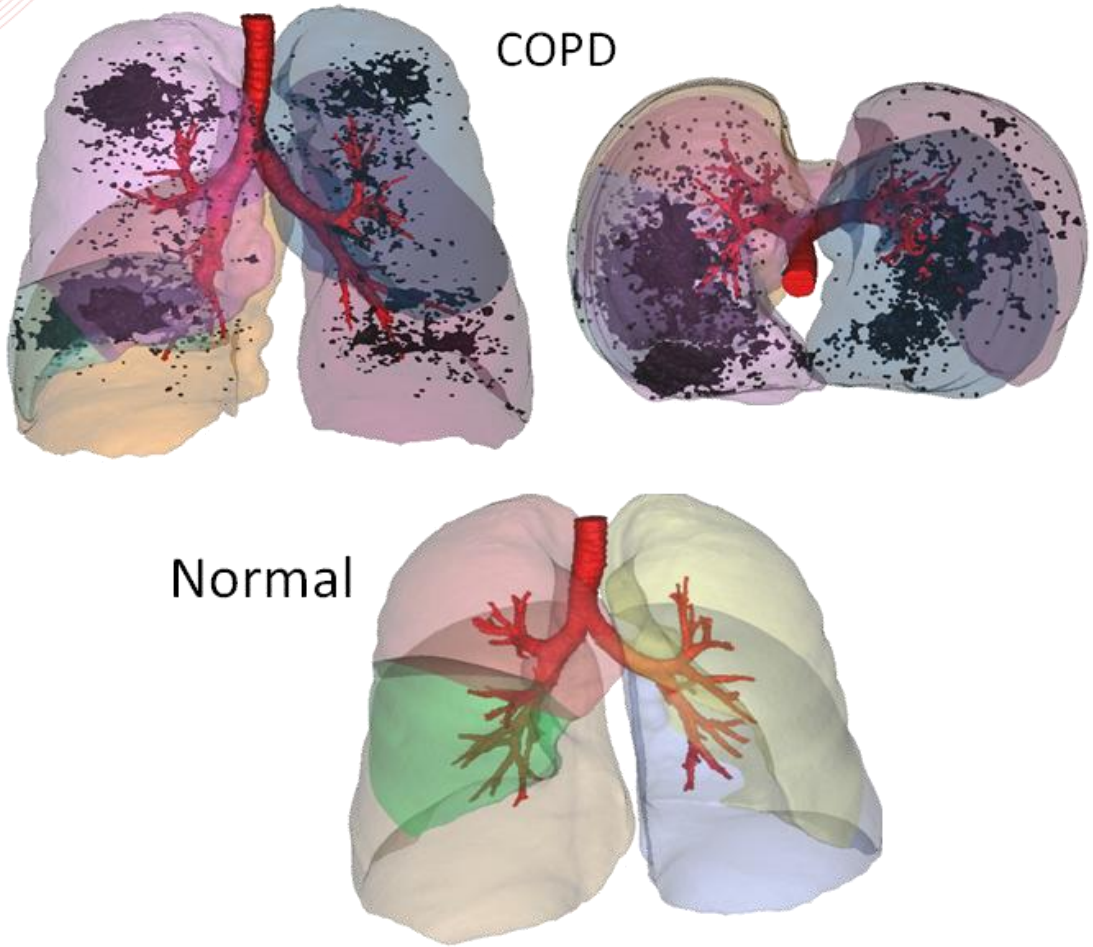
FLUIDDA

FRI: PERFUSION

Emphysema

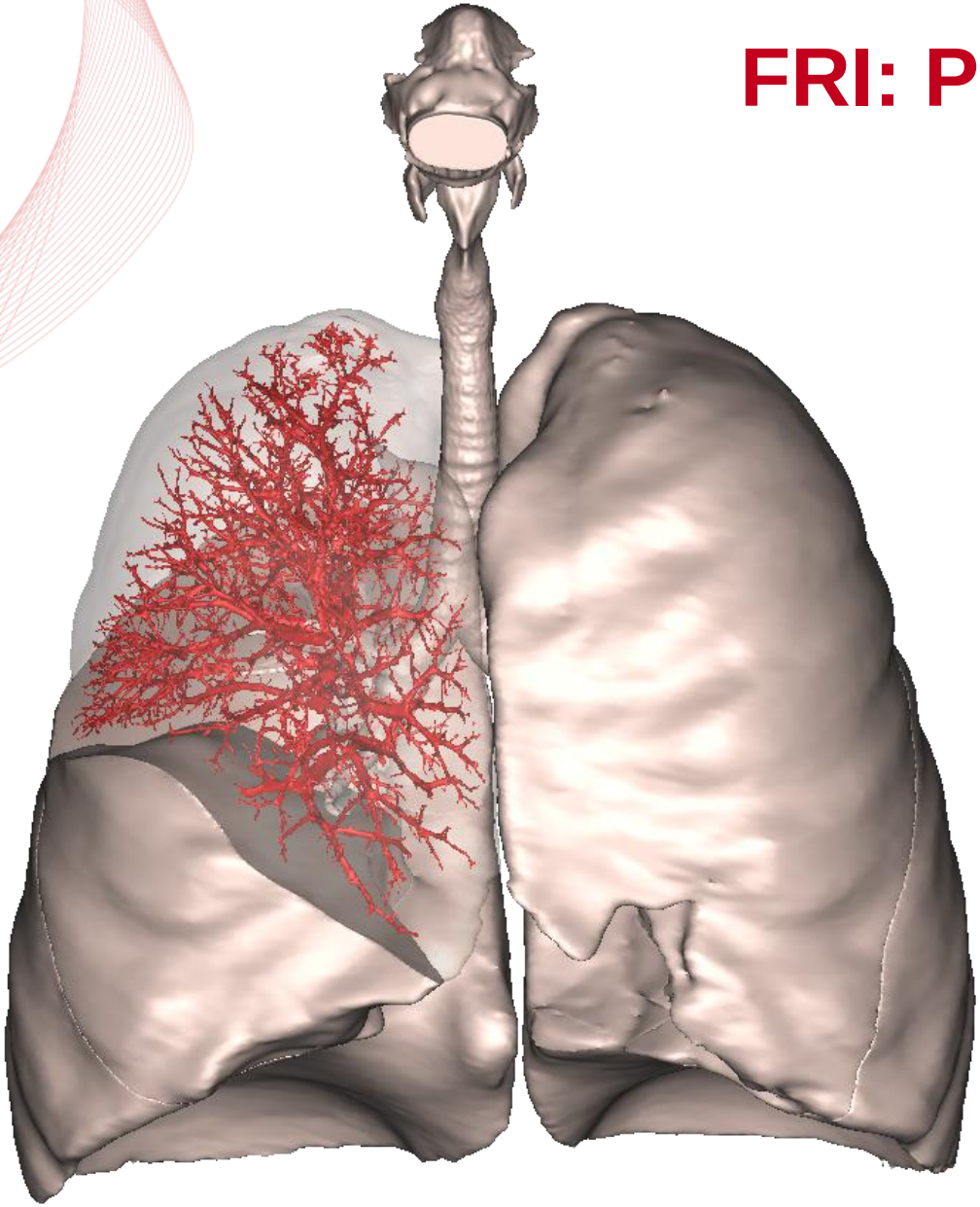


Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

FLUIDDA

FRI: PERFUSION

Blood Vessels

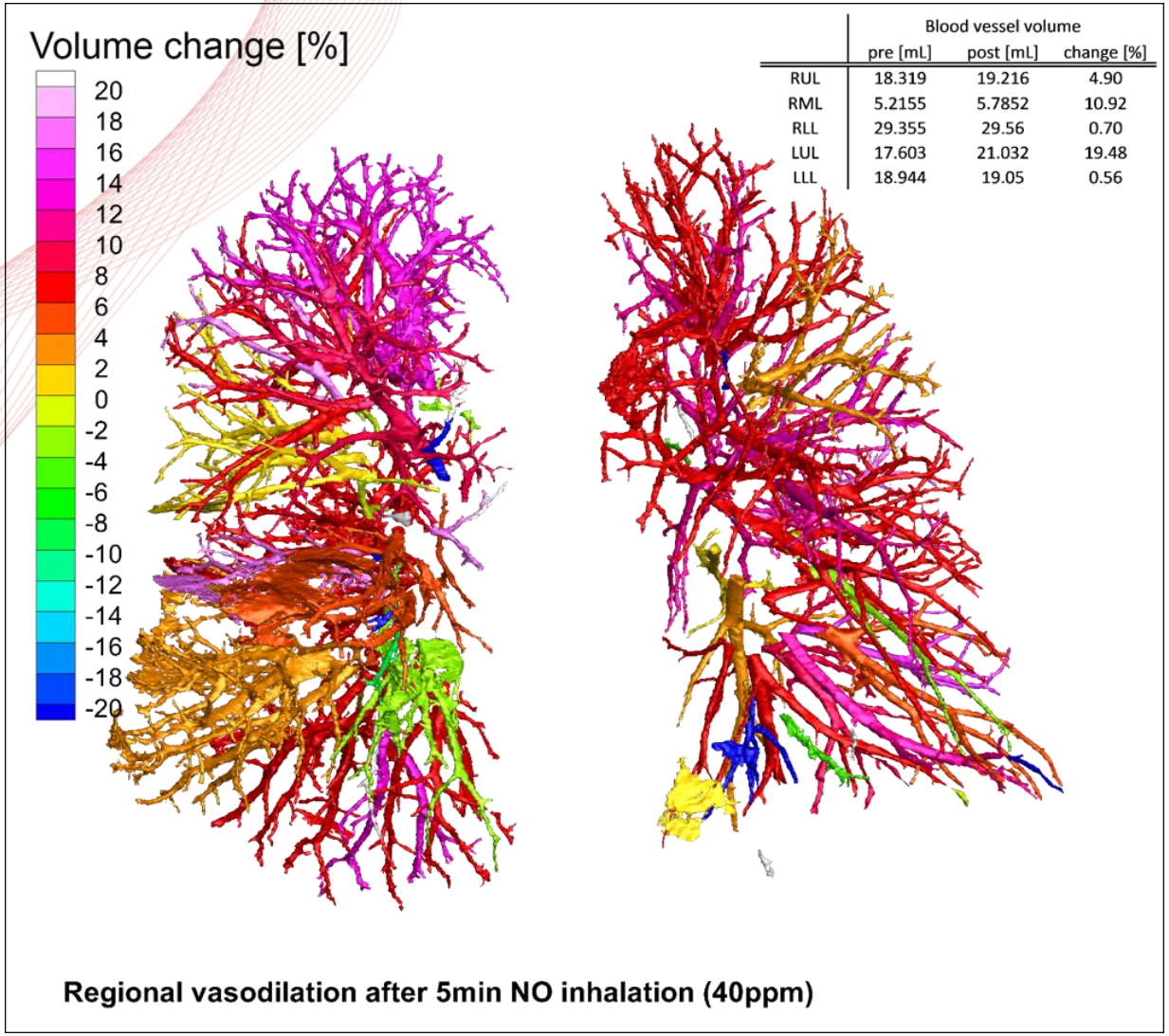


Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

FLUIDDA

FRI: PERFUSION

Blood Vessels



	Blood vessel volume		
	pre [mL]	post [mL]	change [%]
RUL	18.319	19.216	4.90
RML	5.2155	5.7852	10.92
RLL	29.355	29.56	0.70
LUL	17.603	21.032	19.48
LLL	18.944	19.05	0.56

Regional vasodilation after 5min NO inhalation (40ppm)

Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

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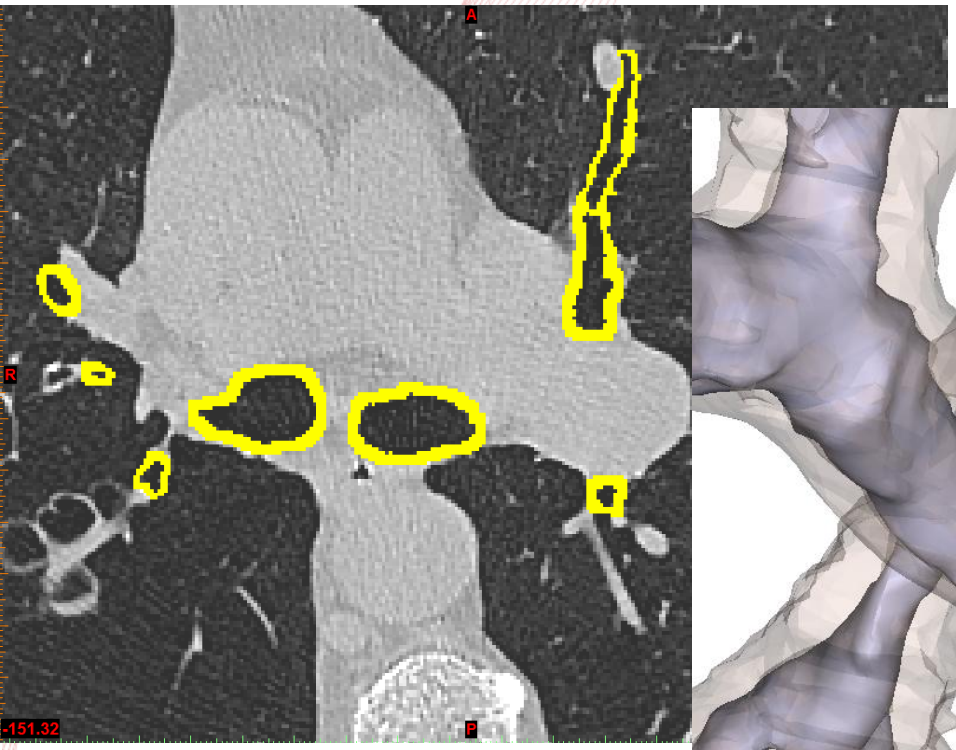
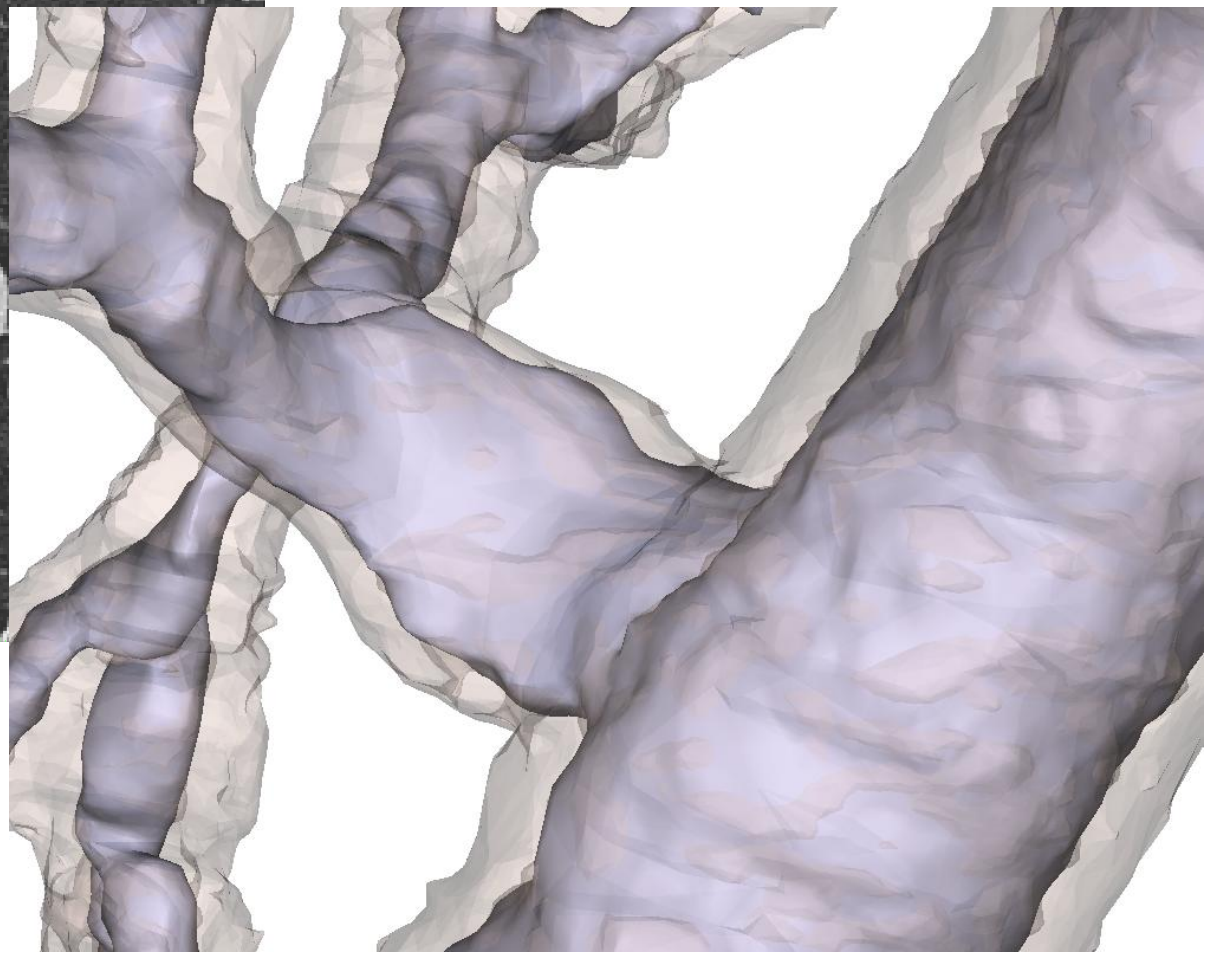
FRI: TISSUE

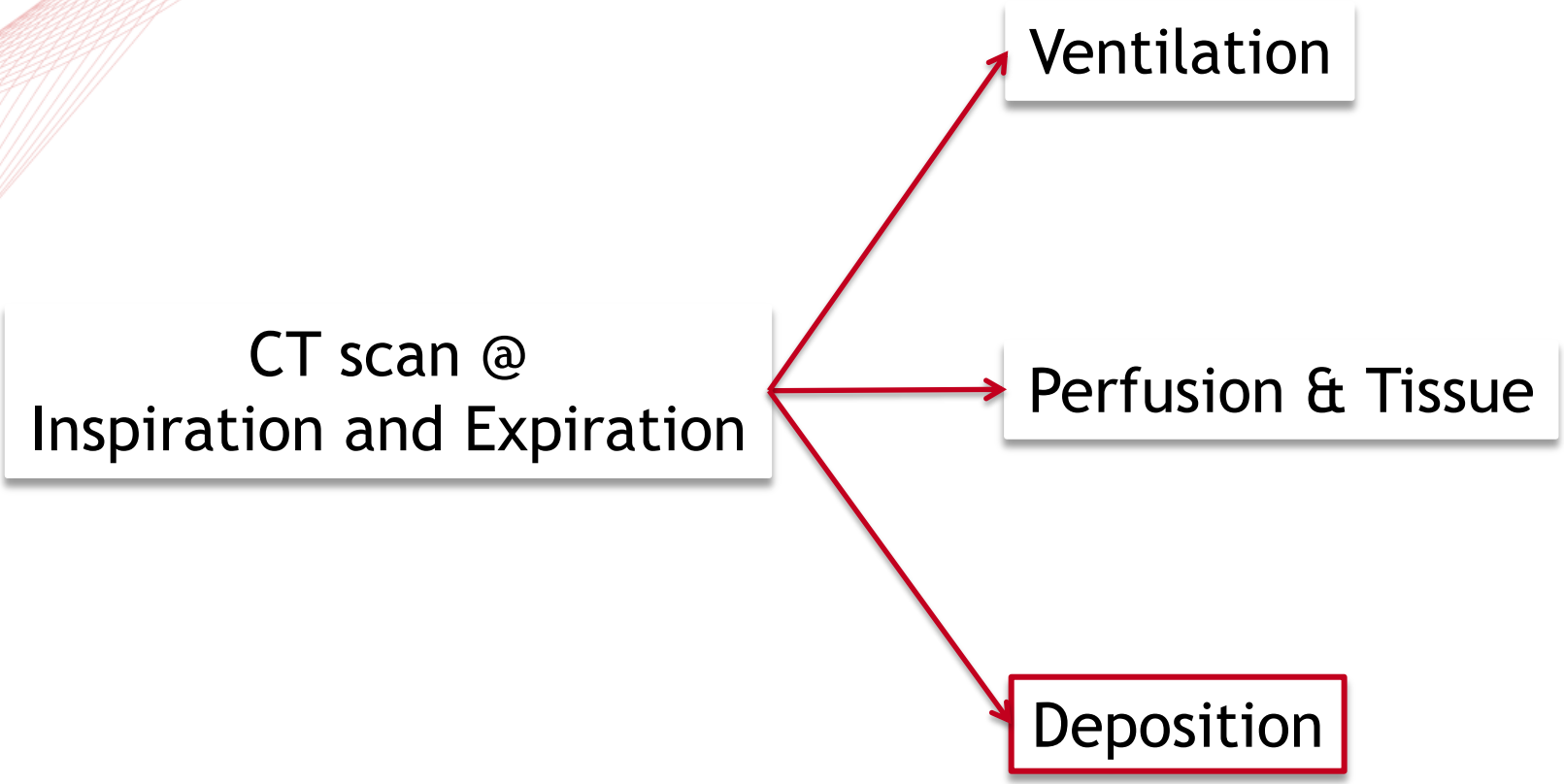
Airway Wall Thickness





Patents EU 09161455.2 US 61/182.493 US 7.540.843 PCT/EP2005/010730

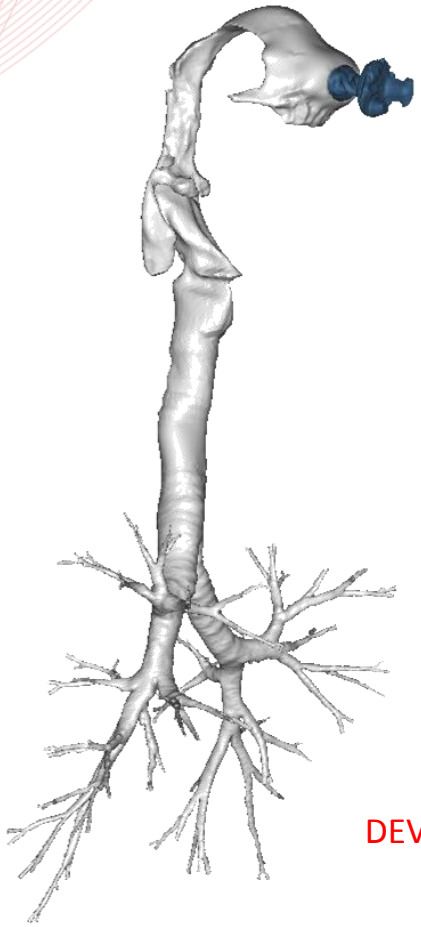
FRI OUTCOME PARAMETERS



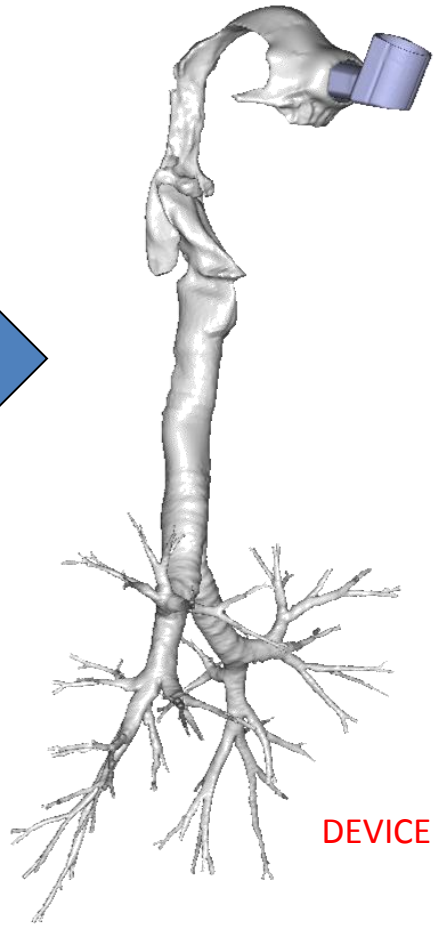
FLUIDDA

FRI: DEPOSITION

Aerosol Simulation



DEVICE A

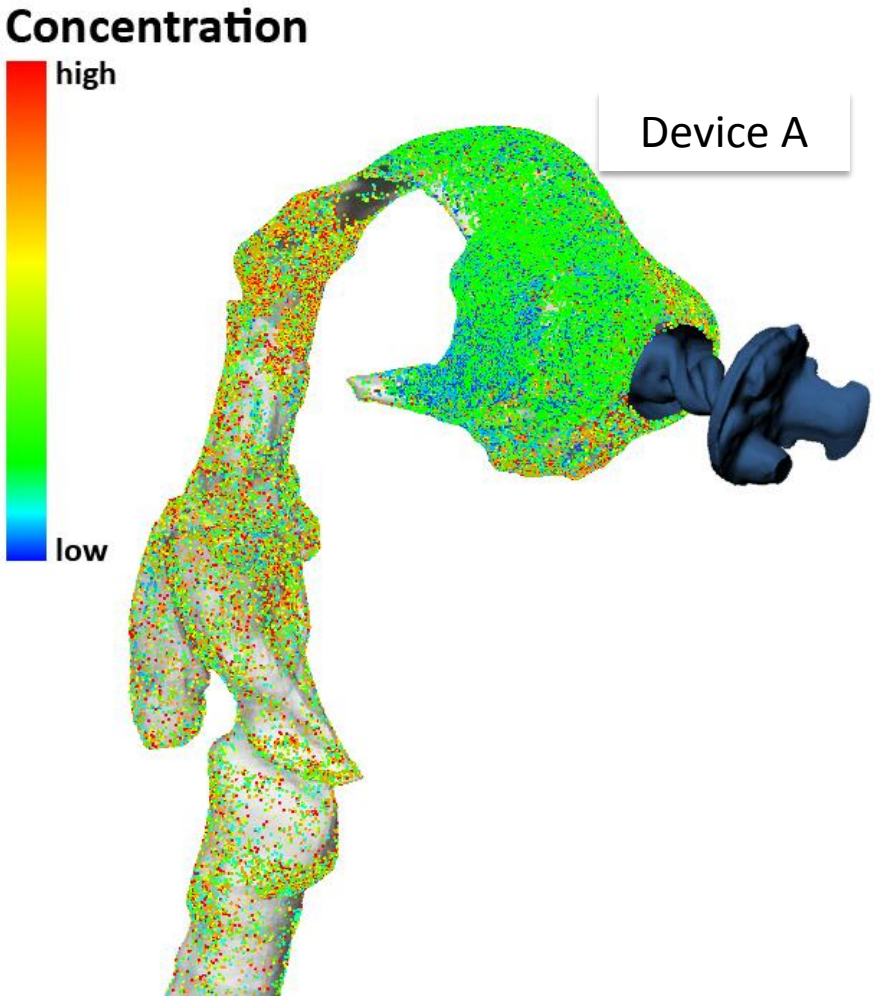


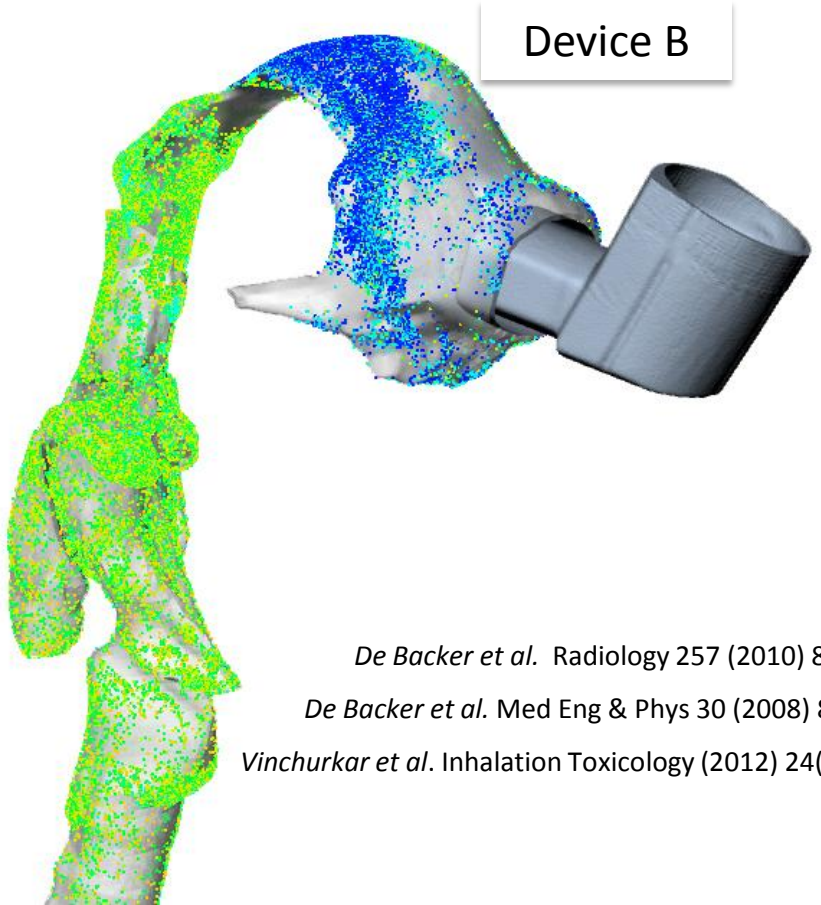
DEVICE B

FLUIDDA

FRI: DEPOSITION

Aerosol Simulation





De Backer et al. Radiology 257 (2010) 854–862

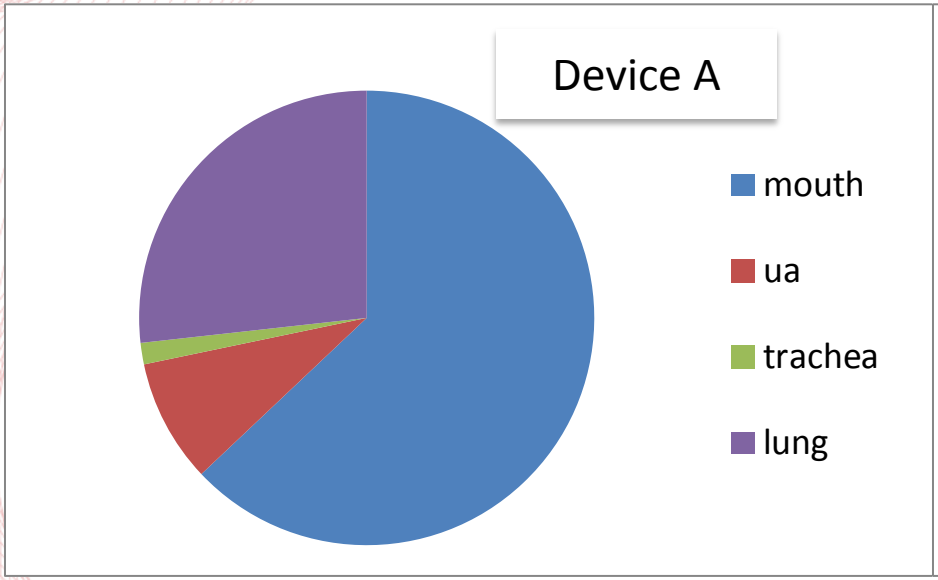
De Backer et al. Med Eng & Phys 30 (2008) 872-879

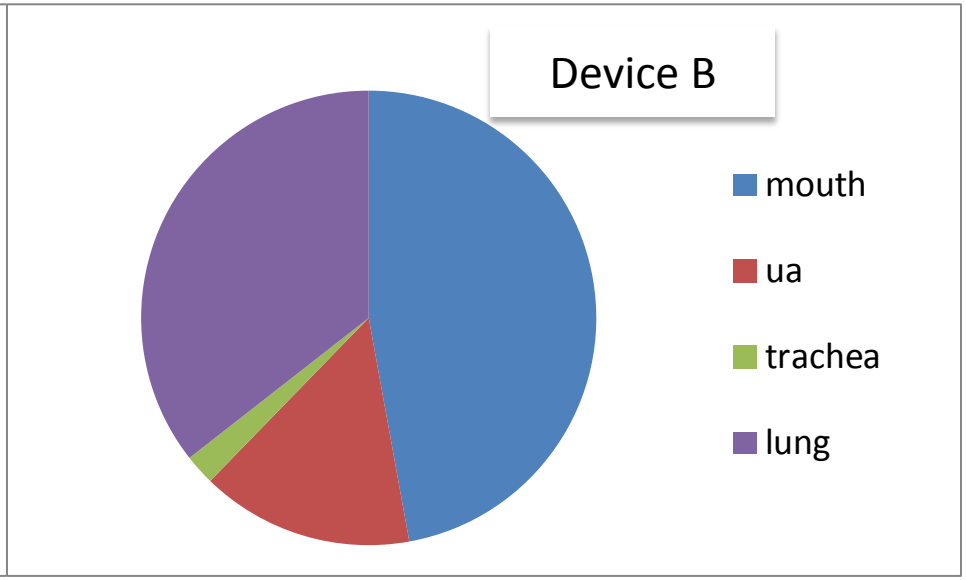
Vinchurkar et al. Inhalation Toxicology (2012) 24(2): 81-8

FRI: DEPOSITION

Aerosol Simulation

- Lung deposition increases by 9%





FRI: DEPOSITION

Aerosol Simulation

Figure 5

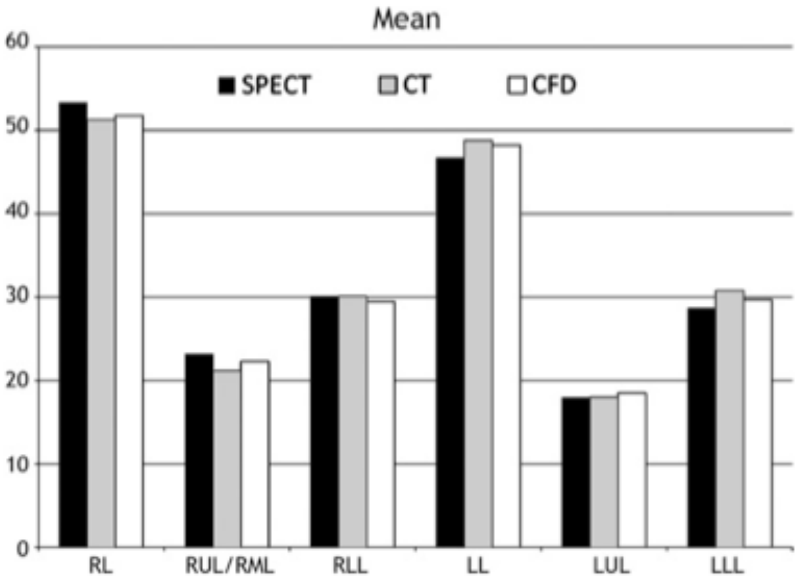
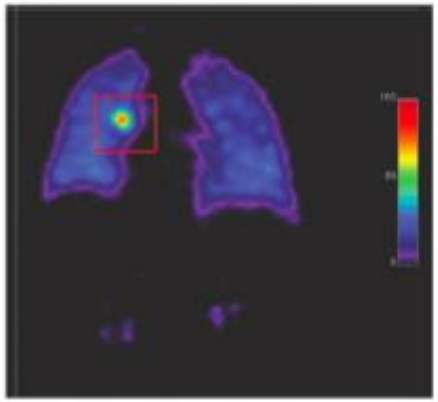


Figure 5: Graph shows airflow distribution (measured as percentage of inhaled air), as determined with SPECT/CT, CT, and CFD, indicating limited differences between all methods. *RL* = right lung, *RUL/RML* = right upper and right middle lobes, *RLL* = right lower lobe, *LL* = left lung, *LUL* = left upper lobe, *LLL* = left lower lobe.

CFD



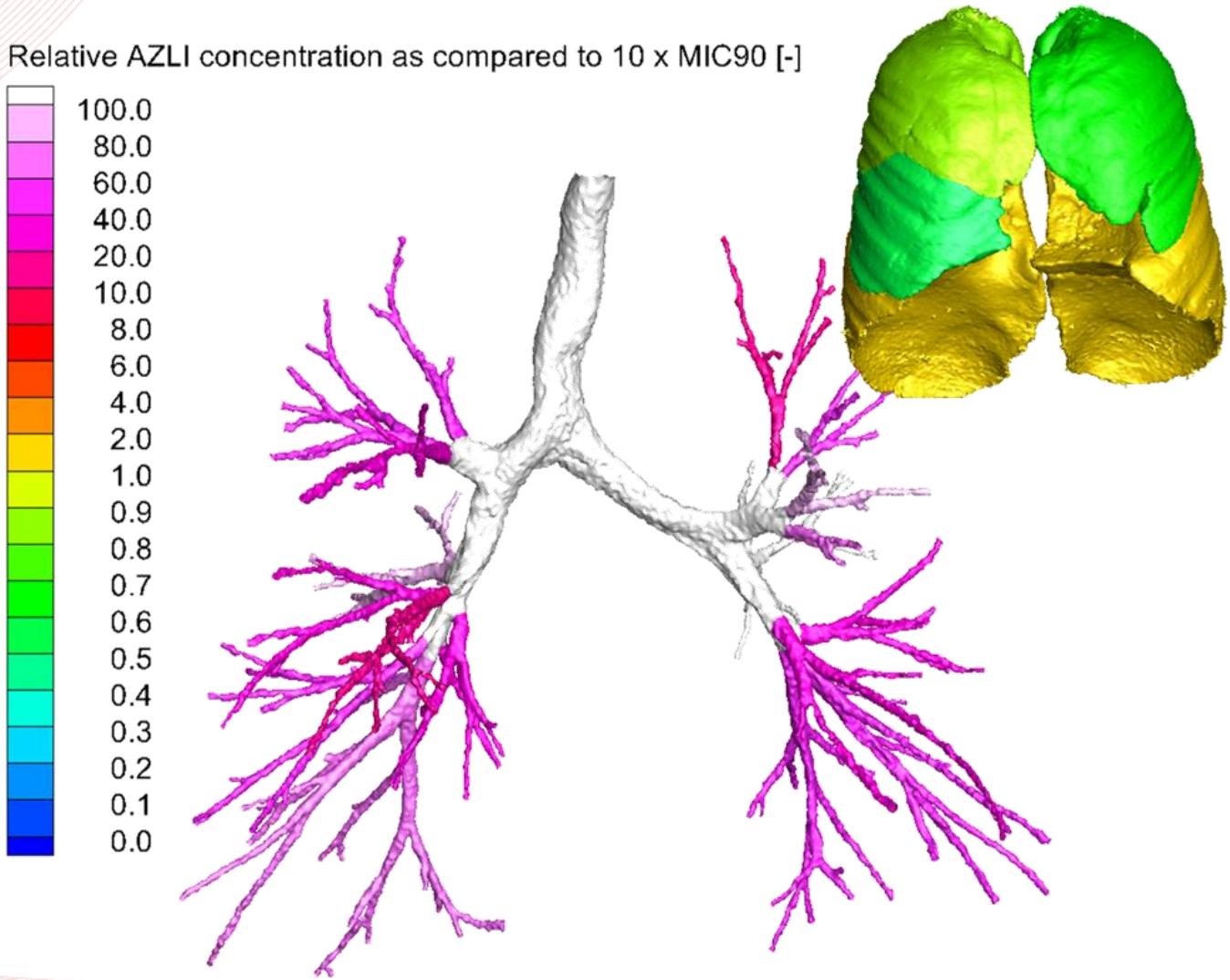
SPECT

De Backer et al. Radiology. 2010 Dec;257(3):854-62.

FRI: DEPOSITION

Aerosol Simulation

Regional concentration relative to a minimal inhibitory concentration threshold for inhaled antibiotics



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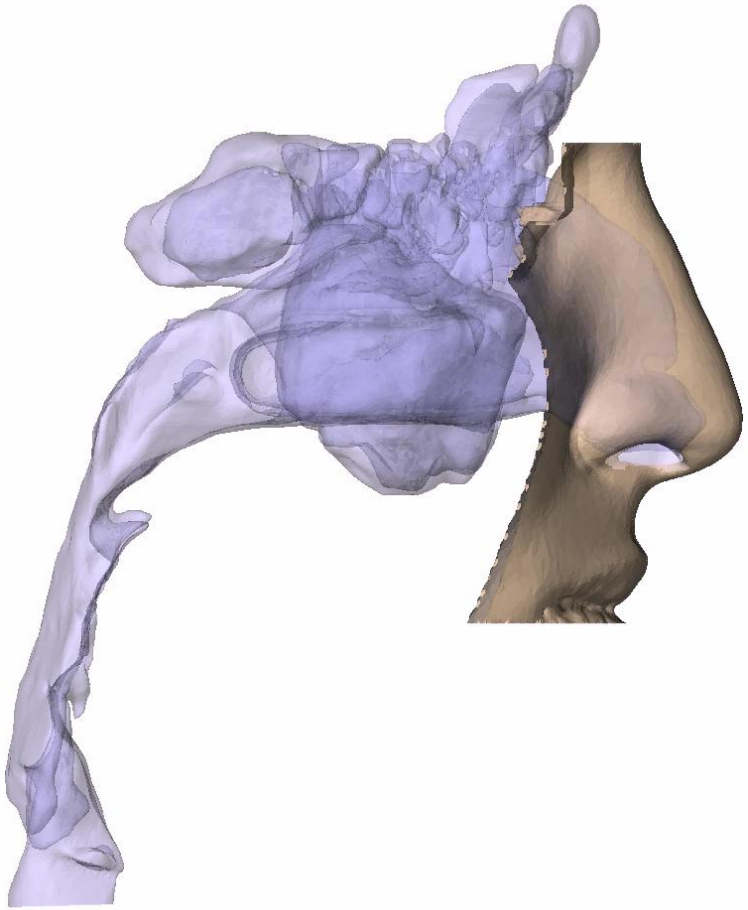
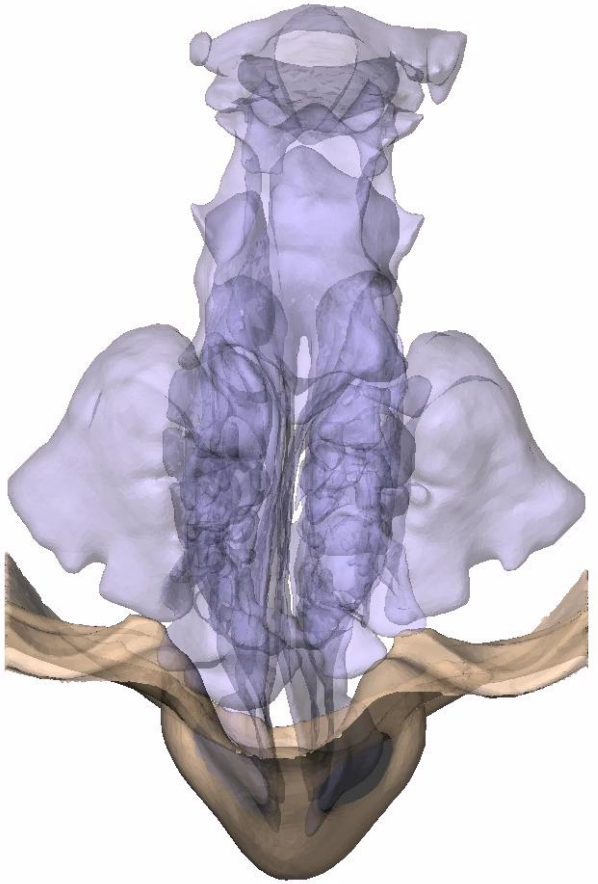
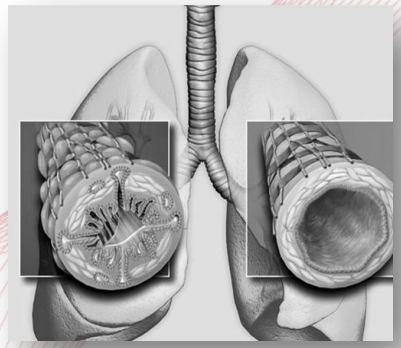
FRI: DEPOSITION

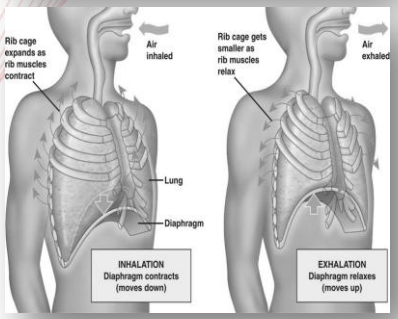
Aerosol Simulation





FROM MODE OF ACTION TO CLINICAL BENEFIT

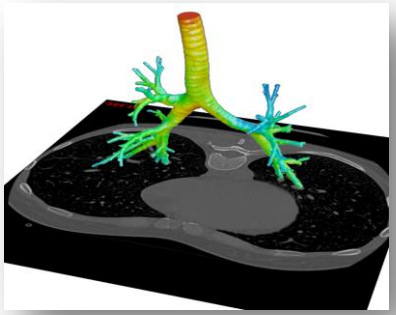




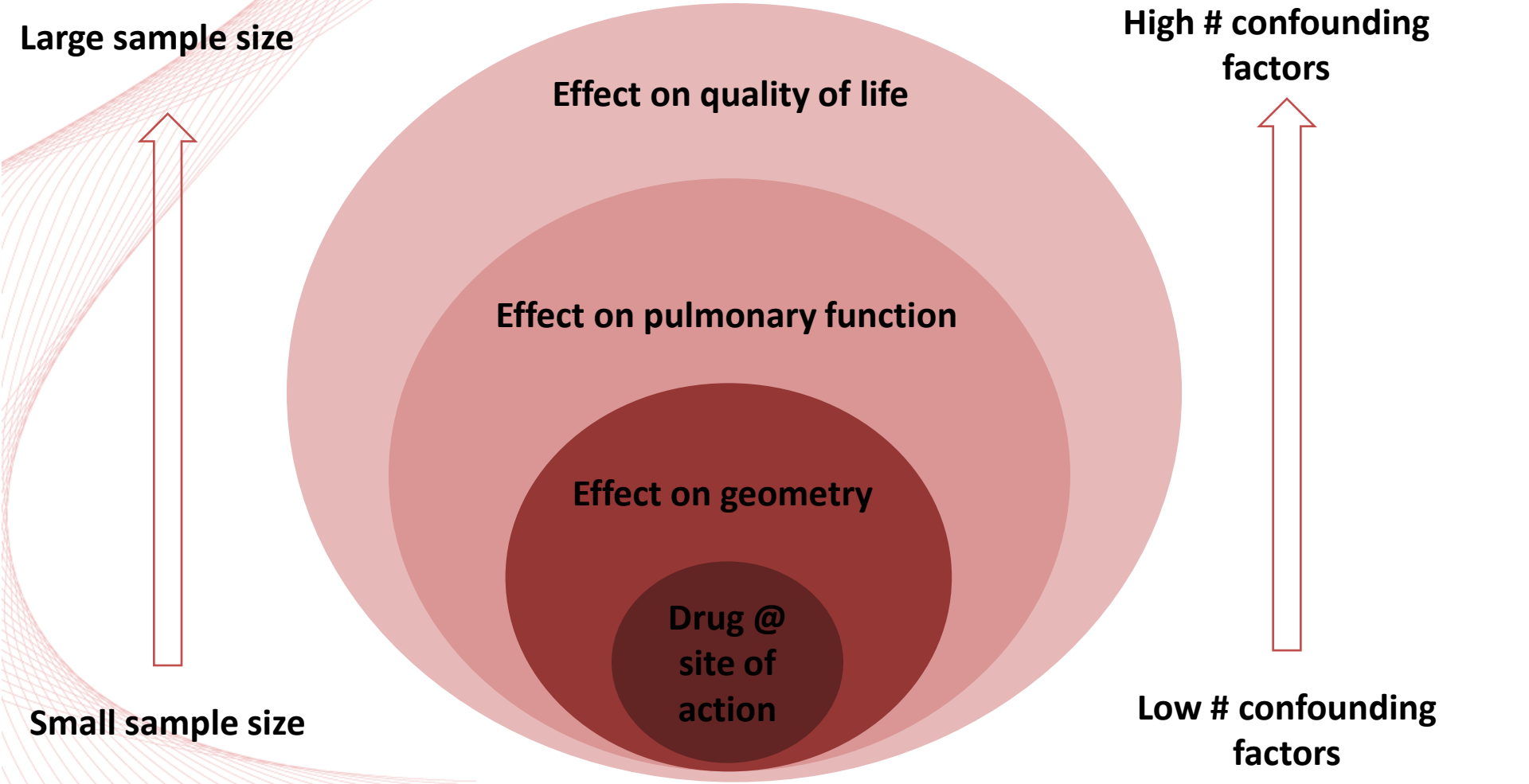
GEOMETRY

PULMONARY FUNCTION

PATIENT'S QUALITY OF LIFE

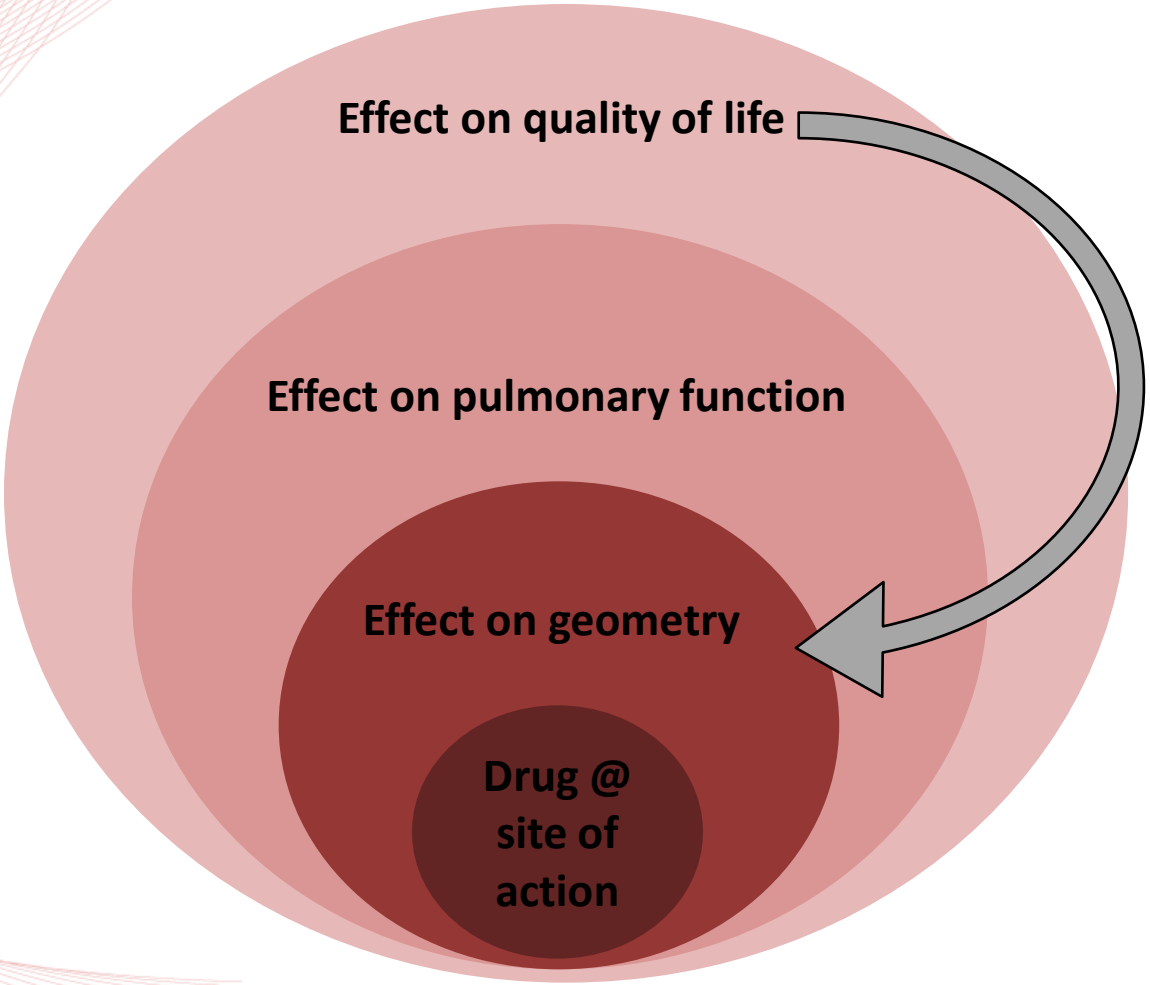


FROM MODE OF ACTION TO CLINICAL BENEFIT

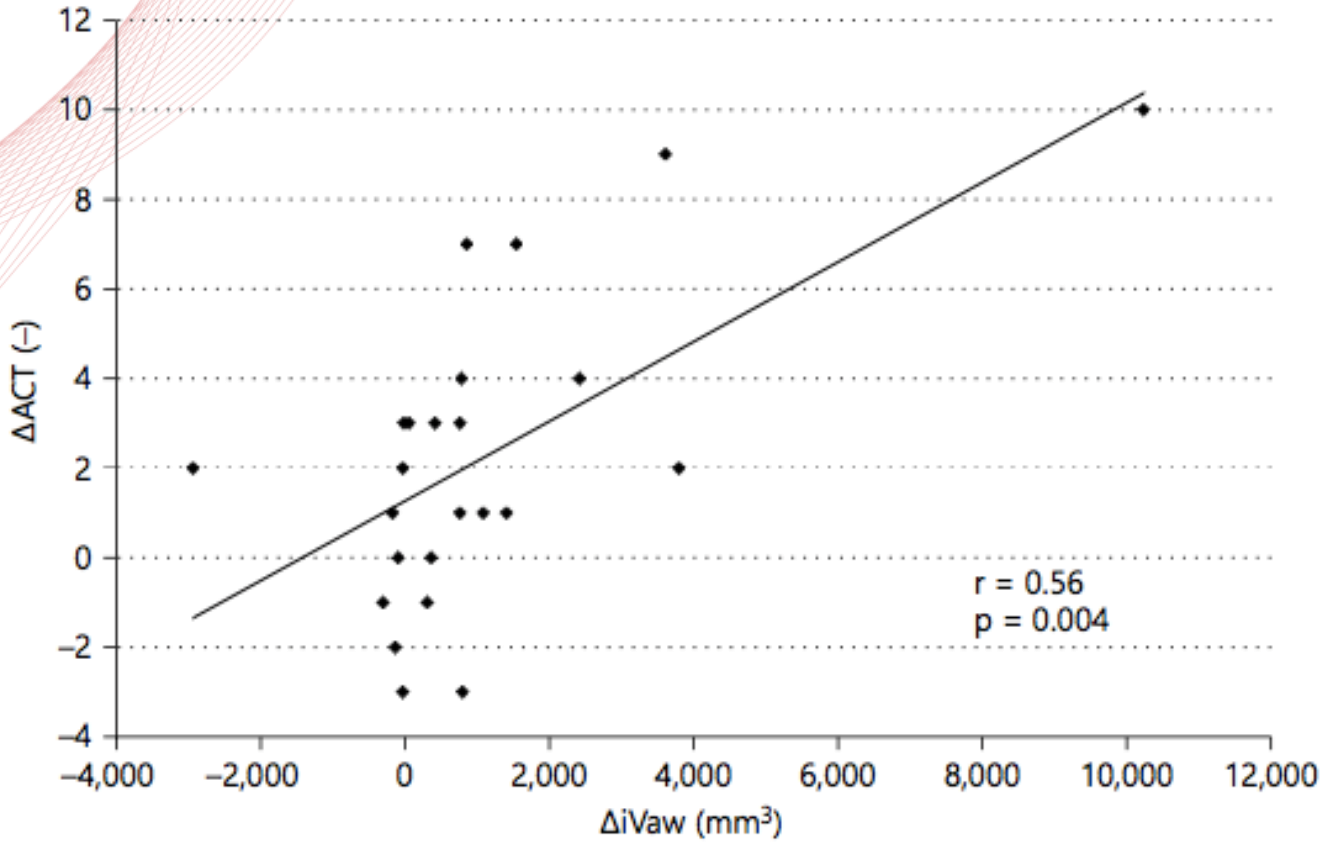


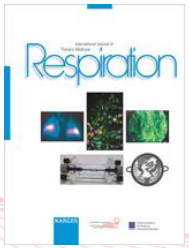
FLUIDDA

CORRELATION BETWEEN GEOMETRY AND QOL



CORRELATION BETWEEN GEOMETRY AND QOL





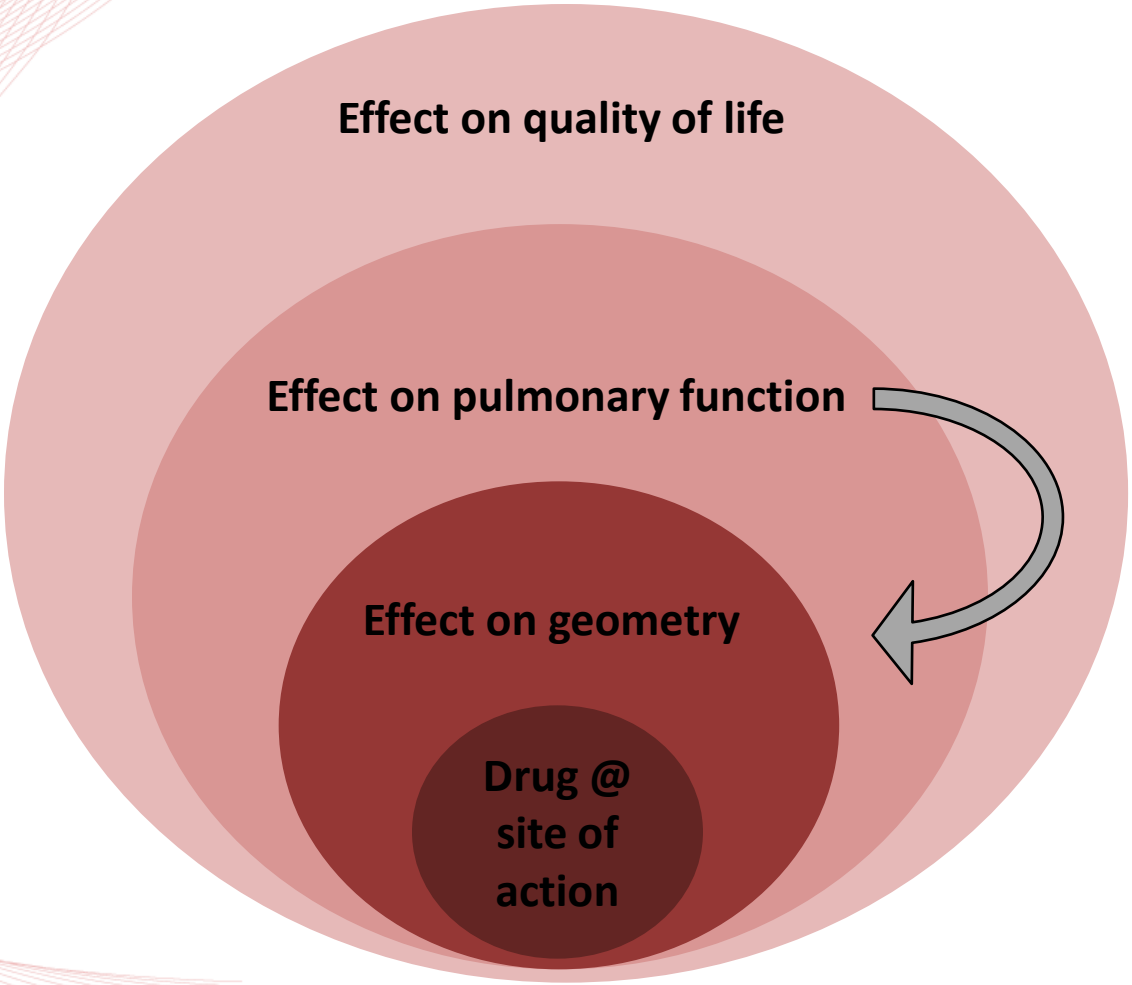
Wim Vos, Jan De Backer, Gianluigi Poli, Annick De Volder, Liesbeth Ghys, Cedric Van Holsbeke, Samir Vinchurkar, Lieve De Backer, Wilfried De Backer

Use of novel functional imaging methods for the assessment of long-term changes in small airways of patients treated with extrafine beclomethasone / formoterol

Respiration 2013

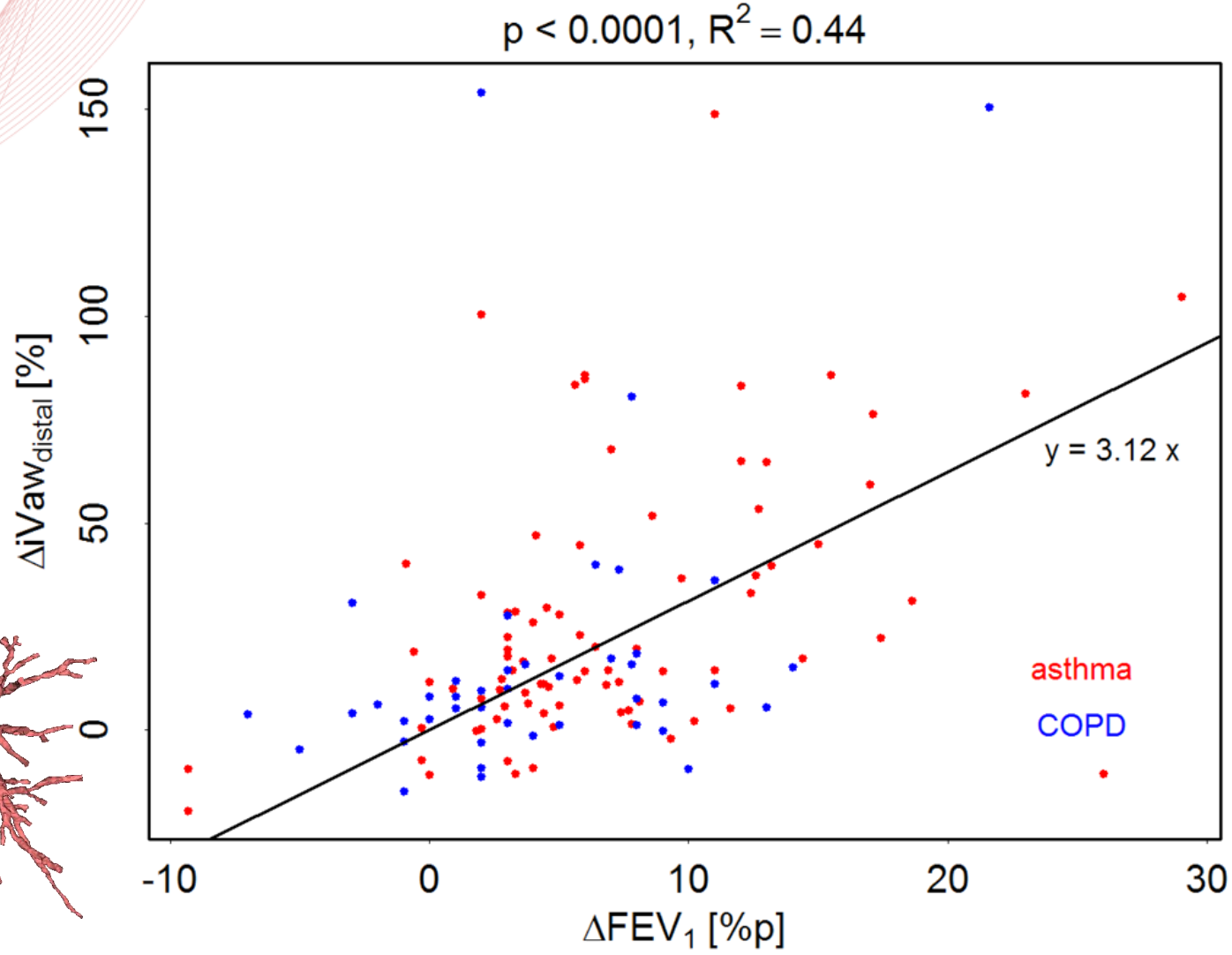
FLUIDDA

CORRELATION BETWEEN GEOMETRY AND PFT



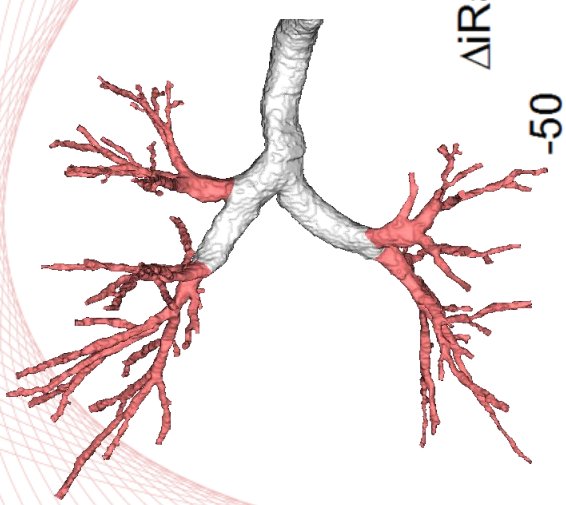
FLUIDDA

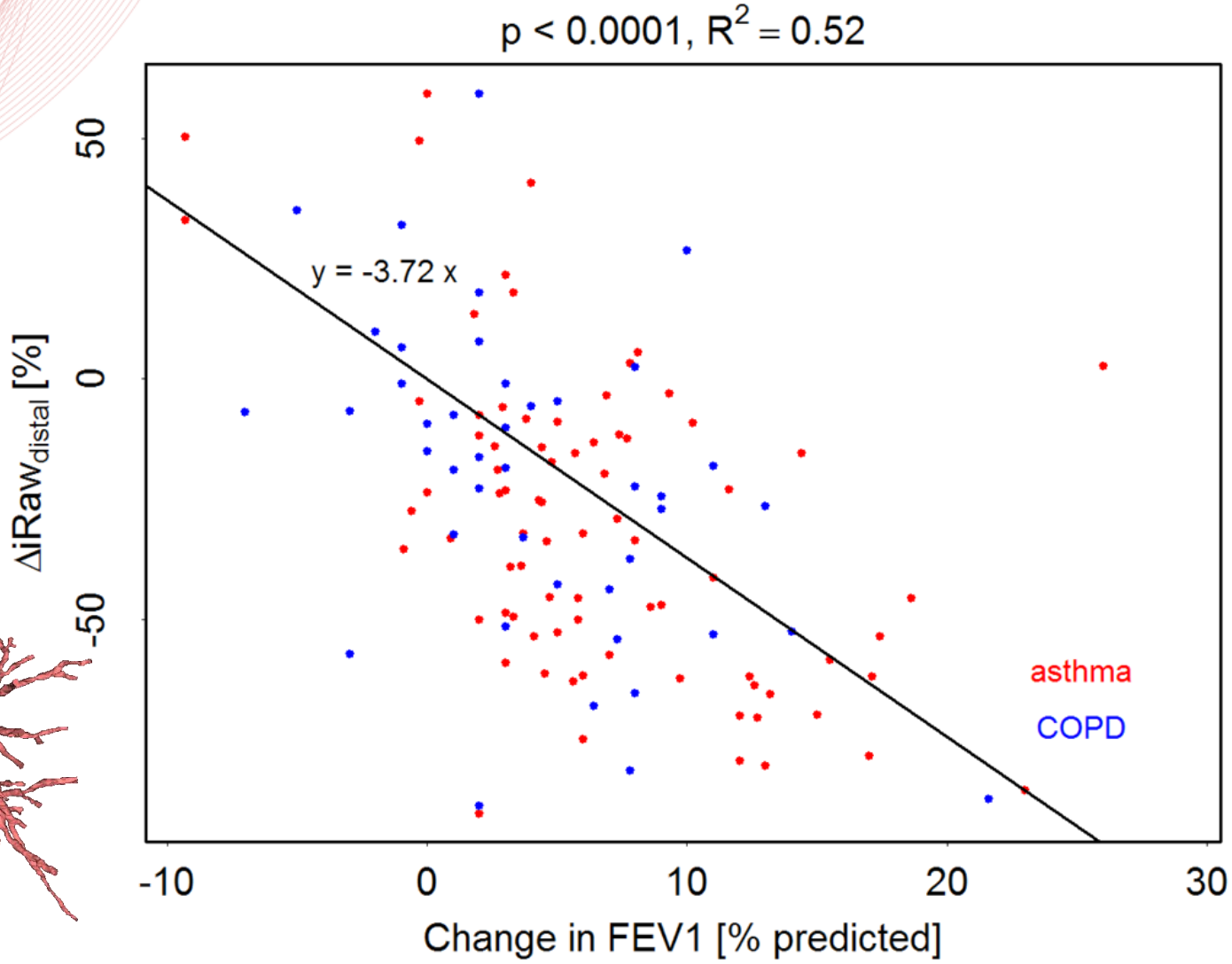
CORRELATION BETWEEN GEOMETRY AND PFT



FLUIDDA

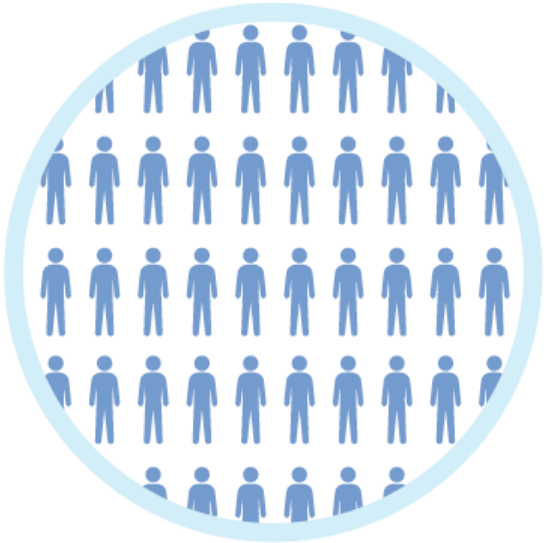
CORRELATION BETWEEN GEOMETRY AND PFT





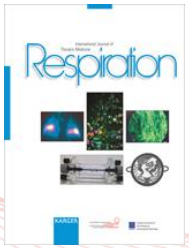
SAMPLE SIZE CALCULATION

Asthma Study



Spirometry **68**

FRI **25**



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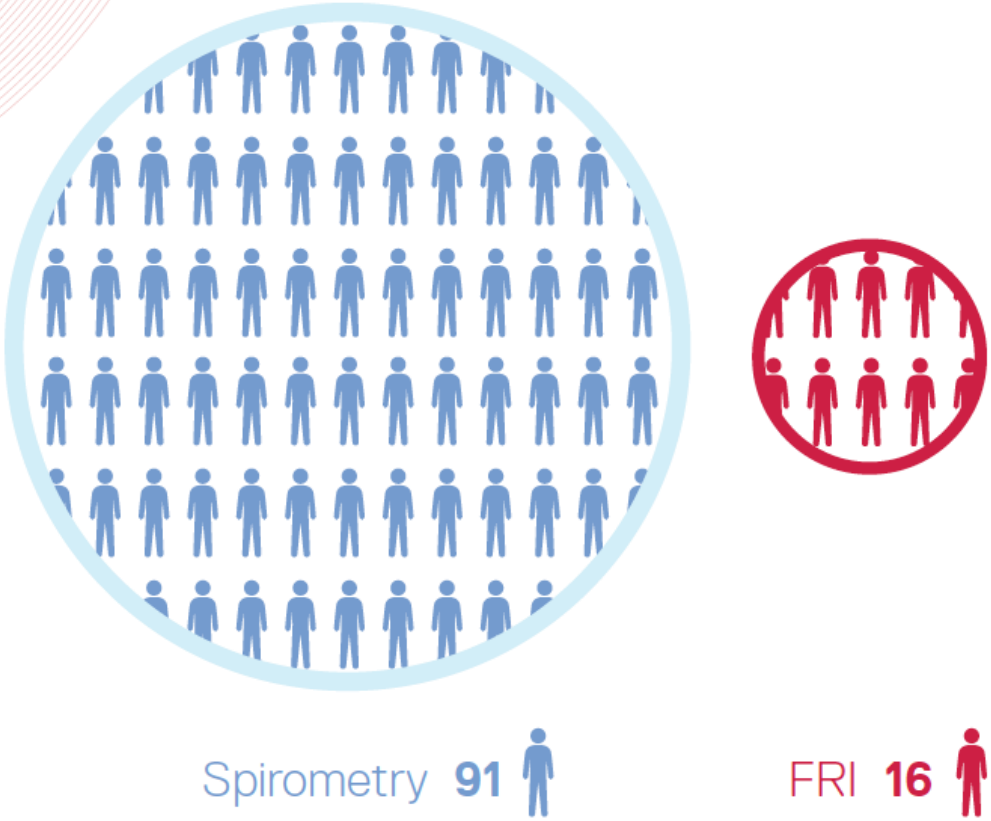
Use of novel functional imaging methods for the assessment of long-term changes in small airways of patients treated with extrafine beclomethasone / formoterol

Respiration 2013

SAMPLE SIZE CALCULATION

COPD Study



Lieve De Backer, Wim Vos, Jan De Backer, Cedric Van Holsbeke, Samir Vinchurkar, Wilfried De Backer

Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests

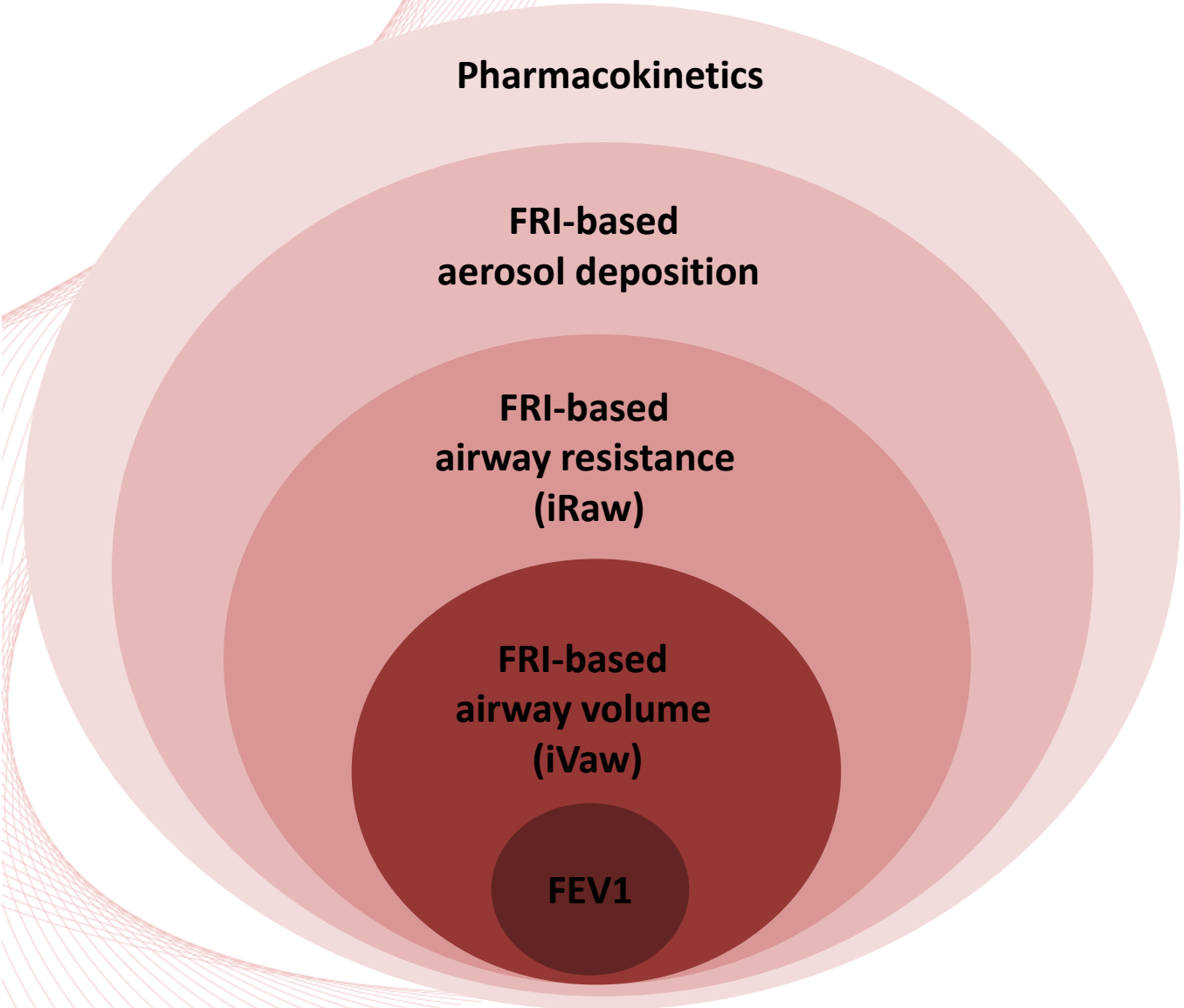
Eur Respir J 2012; 40: 298-305

FLUIDDA

OVERVIEW

- **Functional Respiratory Imaging (FRI)**
  - FRI outcome parameters
  - Added value in drug and device development
- **Bio-equivalence**
  - Salmeterol/Fluticasone branded vs generic in asthma
  - Salbutamol vs Ipratropium Bromide in COPD
- **Conclusions**

FRI TO BRIDGE BETWEEN PK AND PD



High ability to differentiate products

Low ability to differentiate products

FLUIDDA

PROJECT OUTLINE

- double blind, double dummy, randomized, two-way cross-over study
- compare the effects of
  - TEST = Seretide® Evohaler (supplied by Allen & Hanburys, UK)
  - REFERENCE = generic salmeterol/fluticasone HFA pMDI (manufactured by Cipla Ltd, India)
- functional respiratory imaging parameters
- in 16 asthmatic patients

FLUIDDA

ENDPOINTS

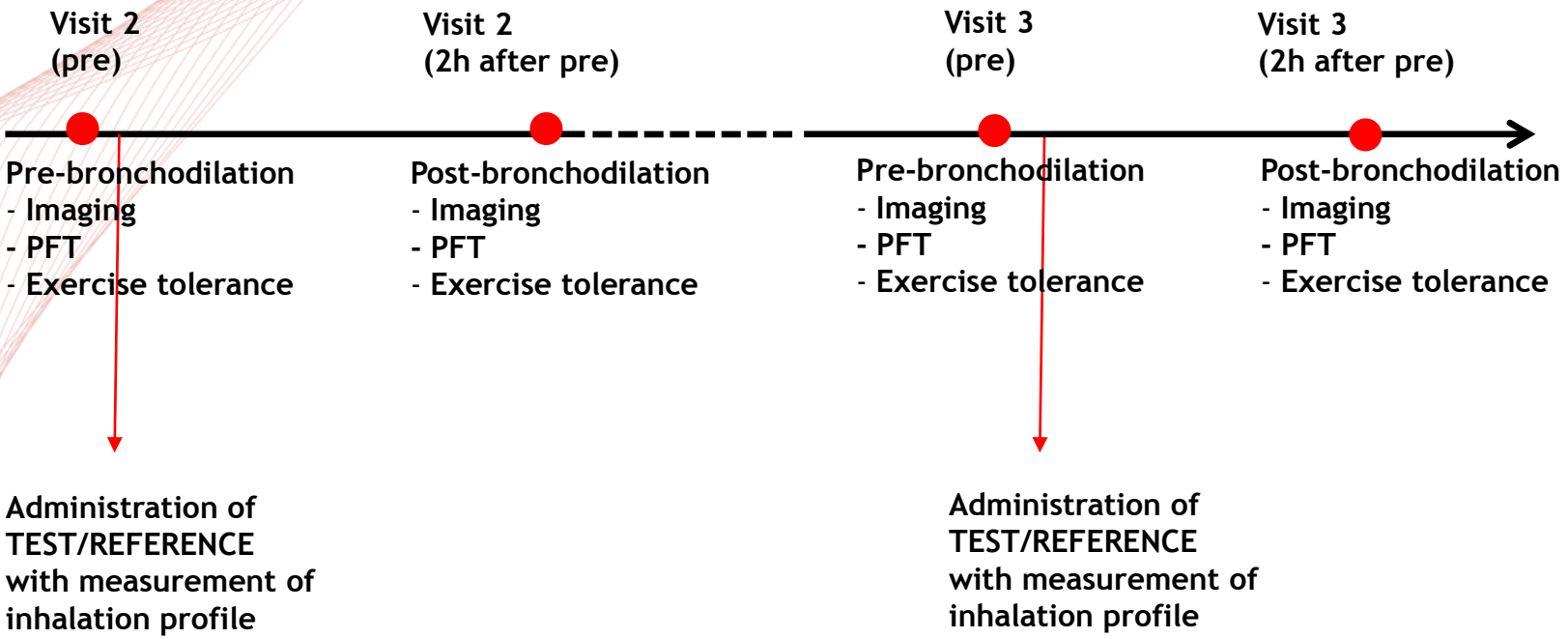
- Primary:

  To evaluate the effect of both study drugs under investigation on FRI parameters and to evaluate the particle deposition in the lungs using CFD.

- Secondary:

  To assess the effect of salmeterol and fluticasone combination therapy on lung function (spirometry and body plethysmography), on exercise capacity (6MWT) and on dyspnea (Borg CR10 Scale and VAS dyspnea). Furthermore the safety of the 2 study drugs under investigation will be evaluated through monitoring of AEs throughout the study.

CLINICAL STUDY DESIGN



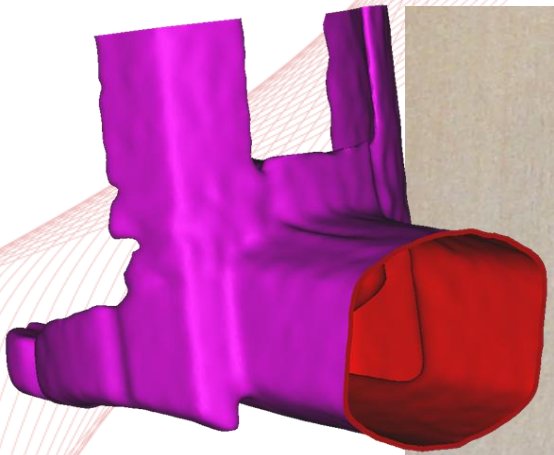
FLUIDDA

DATA COLLECTION

- CT scans:
  - Pre-dose: FRC and TLC
  - Post-dose: TLC
- Inhalation profile:
  - Calibration of respiration belts with pneumotach
  - Measurements during actual inhalation of study drug
- Pulmonary function tests:
  - Spirometry
  - Body plethysmography
  - Exercise tolerance
  - Dyspnea

FLUIDDA

INHALERS



FLUIDDA

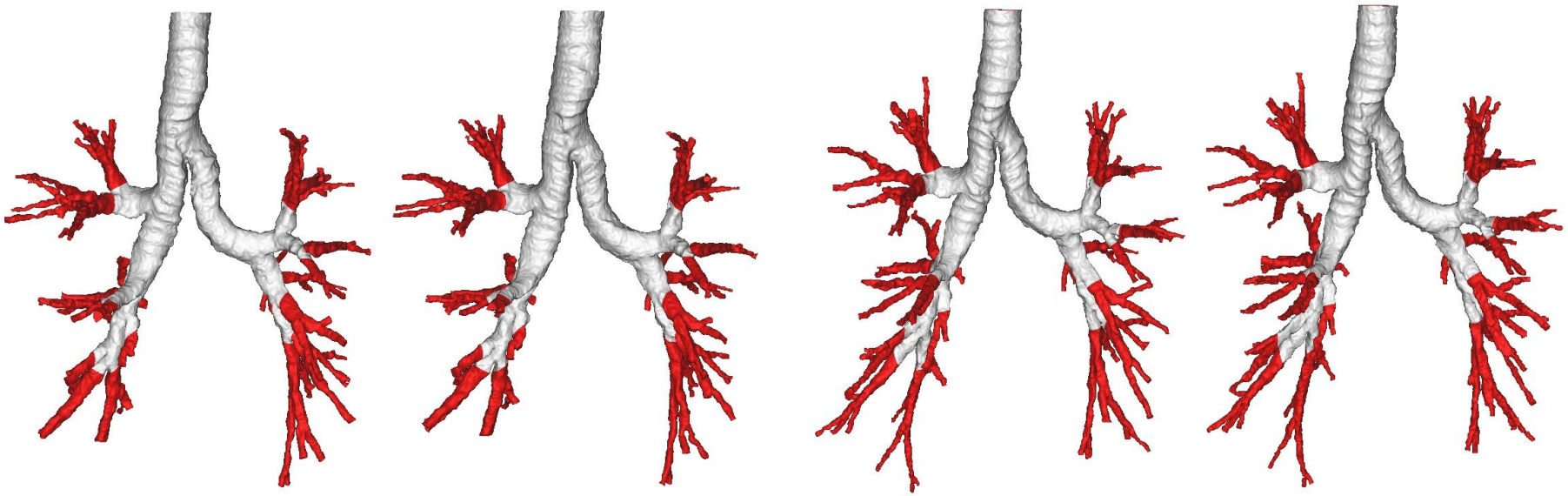
FRI OUTCOME

- Pre-dose/post-dose LA airway models
  - Airway volumes (iVaw)
  - Airway surface area (iSaw)
  - Airway resistance (iRaw)
- Pre-dose internal airflow distribution
  - For CFD boundary conditions
- Pre-dose coupled UA/LA/inhaler models for particle deposition simulations
  - Regional deposition of inhaled compounds

FLUIDDA

FRI OUTCOME

- Pre-dose/post-dose LA airway models



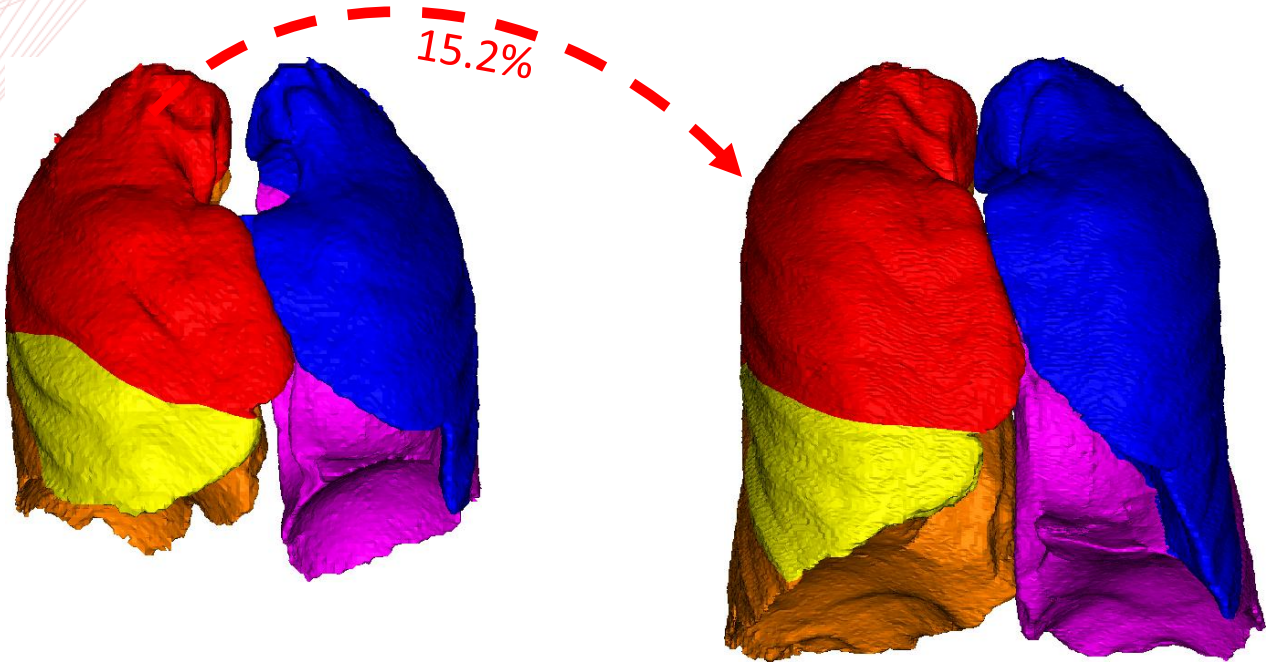
V2_pre V2_post V3_pre V3_post

  - Baseline stability, drug effect, effect comparison

FLUIDDA

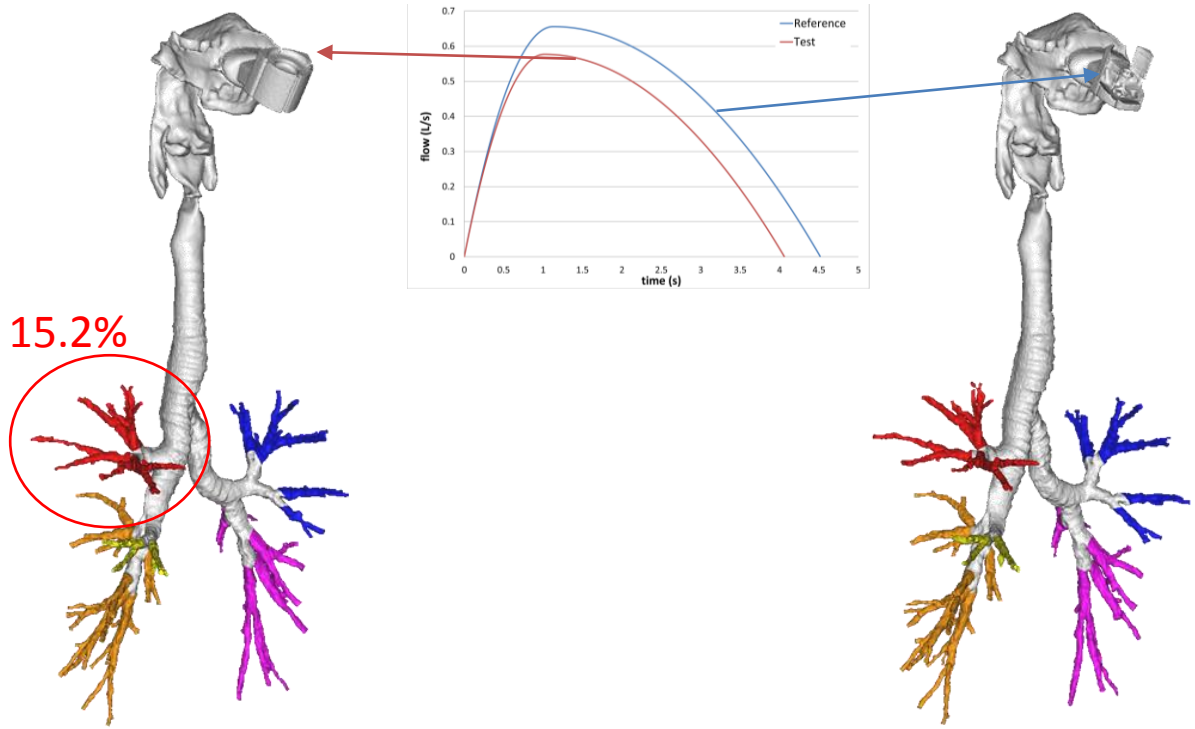
FRI OUTCOME

- Pre-dose internal airflow distribution
  - For CFD boundary conditions



FRI OUTCOME

- Pre-dose coupled UA/LA/inhaler models for particle deposition simulations
  - Regional deposition of inhaled compounds



FLUIDDA

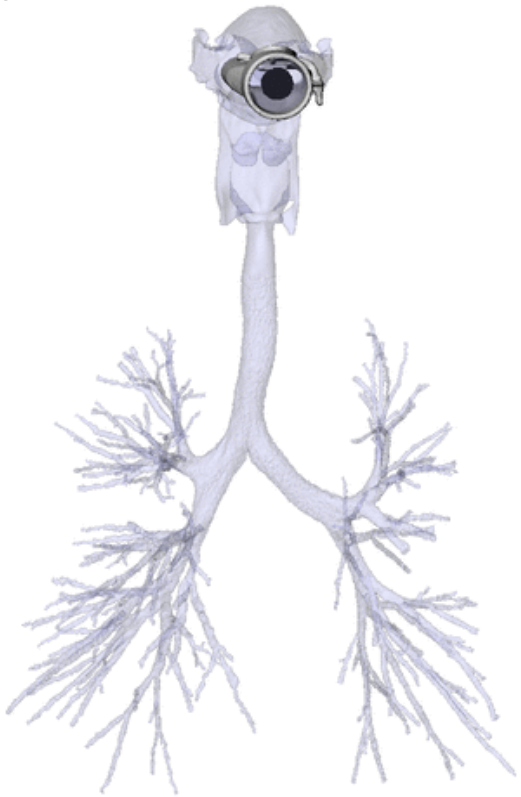
FRI OUTCOME

- Pre-dose coupled UA/LA/inhaler models for particle deposition simulations

- ACI data was used for particle diameter distribution of TEST and REFERENCE

FRI OUTCOME

- Pre-dose coupled UA/LA/inhaler models for particle deposition simulations
  - Regional deposition of inhaled compounds



FLUIDDA

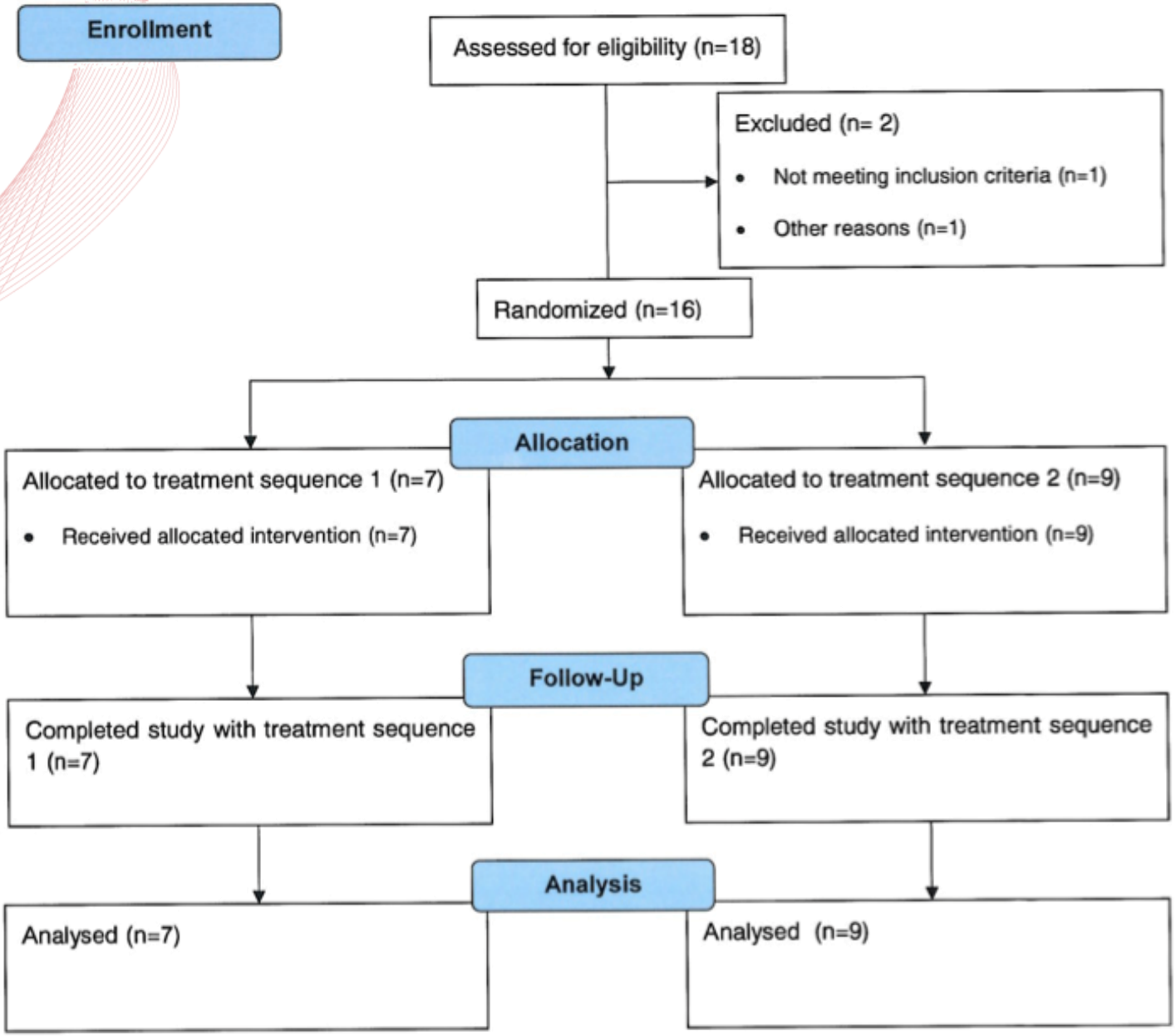
STATISTICS

- To assess whether products are different
  - Wilcoxon matched pairs to assess drug effect
  - Mann Whitney U test to compare drug effects
  - $p<0.05$ for significance
- To assess whether products are equivalent
  - Two one-sided tests
  - 90% confidence interval of Test/Reference ratio
  - Between 80%-125% bounds

IN- AND EXCLUSION CRITERIA

- Inclusion
  - Diagnosed asthma
  - Treated according to GINA guidelines
  - Non or ex-smokers (stopped <1y and <10y total packyears)
- Exclusion
  - Exacerbation during last 8 weeks
  - COPD
  - Upper or lower airway infection
  - Received oral corticosteroids in the last 4 weeks

FLUIDDA


Enrollment
Assessed for eligibility (n=18)
Excluded (n= 2)
Not meeting inclusion criteria (n=1)
Other reasons (n=1)
Randomized (n=16)
Allocation
Allocated to treatment sequence 1 (n=7)
Received allocated intervention (n=7)
Allocated to treatment sequence 2 (n=9)
Received allocated intervention (n=9)
Follow-Up
Completed study with treatment sequence 1 (n=7)
Completed study with treatment sequence 2 (n=9)
Analysis
Analysed (n=7)
Analysed (n=9)

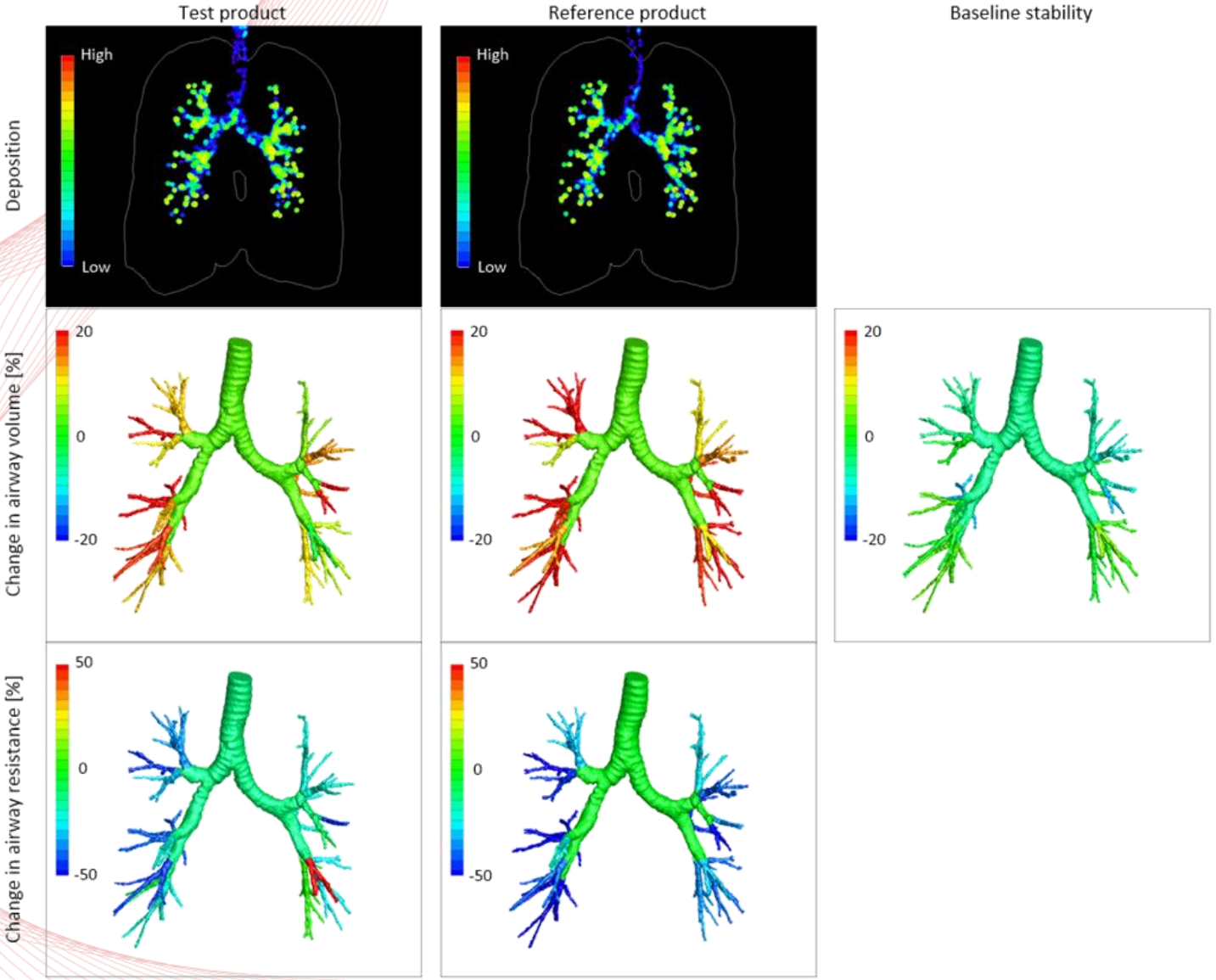
FLUIDDA

PATIENTS

9F/7M	Mean	SD	Min	Max
Age [y]	58.88	8.70	44	73
Height [cm]	169.69	9.46	158	192
Weight [kg]	81.16	16.25	55	102.5
BP Sys [mmHg]	121.44	7.70	107	130
BP Dia [mmHg]	79.94	9.65	60	92
HR [bpm]	70.25	12.73	56	102
FVC [L]	4.23	1.25	2.46	6.74
FVC [%p]	120.53	13.20	90.4	141.9
FEV1 [L]	2.97	0.91	1.77	5.27
FEV1 [%p]	104.50	18.87	65.7	133.9
FEV1/FVC [%]	70.95	9.61	41.7	80.6
PEF [L/s]	8.21	2.71	5.59	15.75
MEF50 [L/s]	2.70	1.37	0.9	6.24
FEF75 [L/s]	0.73	0.38	0.23	1.69
FEF25 [L/s]	5.54	2.33	1.95	11.45
RV [L]	2.50	0.75	1.51	4.14
RV [%p]	116.19	23.77	90	170
TLC [L]	6.84	1.88	4.48	10.65
TLC [%p]	114.44	13.79	91	142
FRC [L]	3.45	0.95	2.06	5.36
FRC [%p]	109.88	18.39	77	149
Raw [kPas/L]	0.328	0.130	0.119	0.640
sRaw [kPas]	1.236	0.533	0.560	2.109
6MWT [m]	605.06	75.15	473	735
6MWT [%p]	92.75	11.96	75	118

FLUIDDA

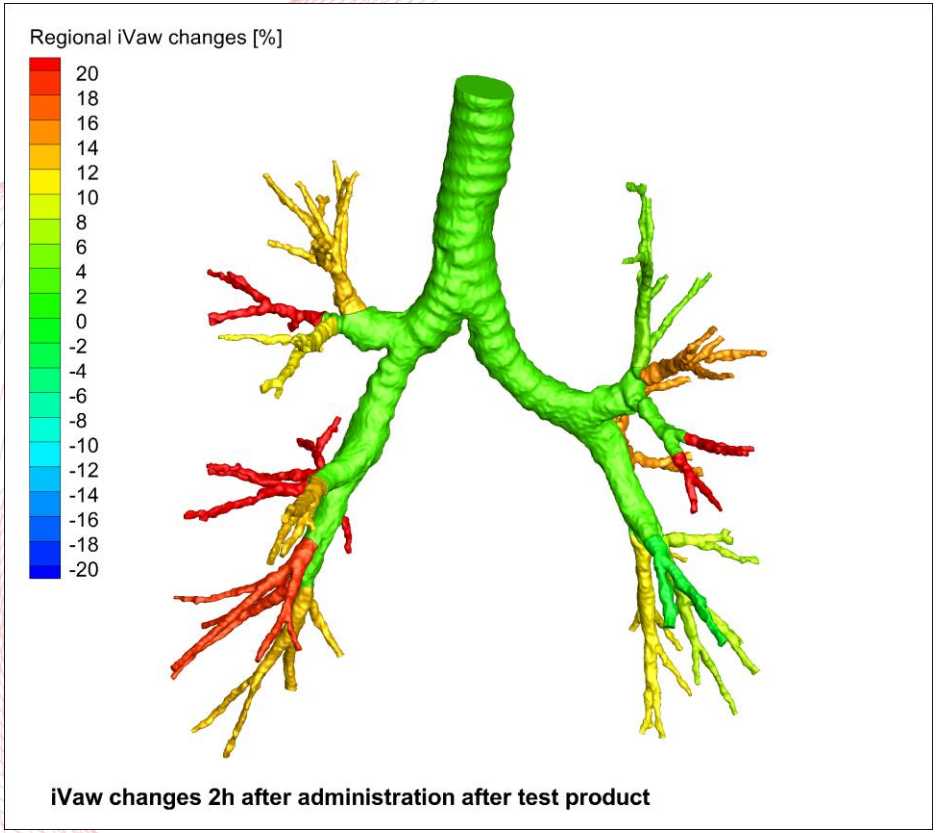
RESULTS



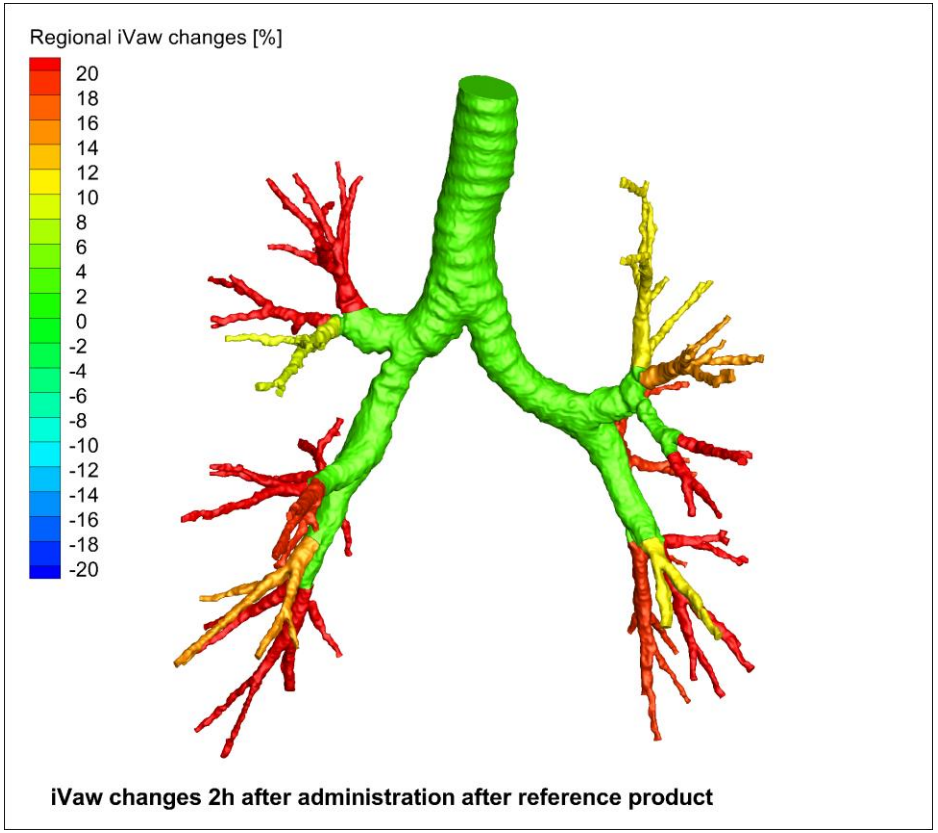
FLUIDDA

RESULTS

- FRI-based airway Volume (iVaw)



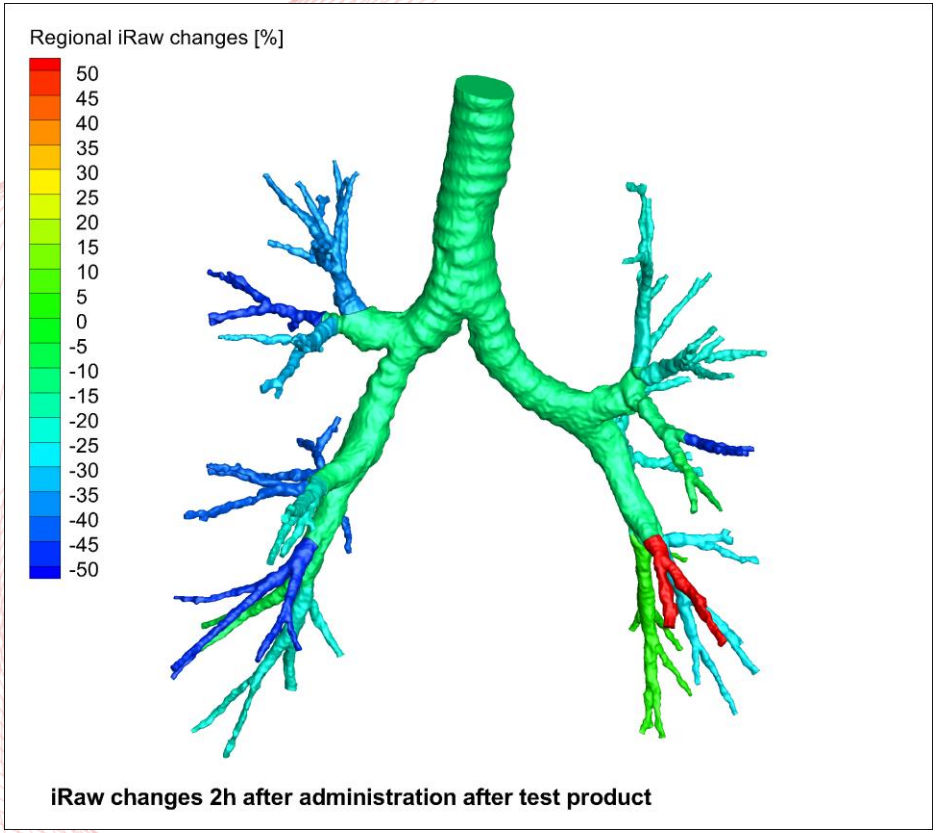
iVaw changes 2h after administration after test product



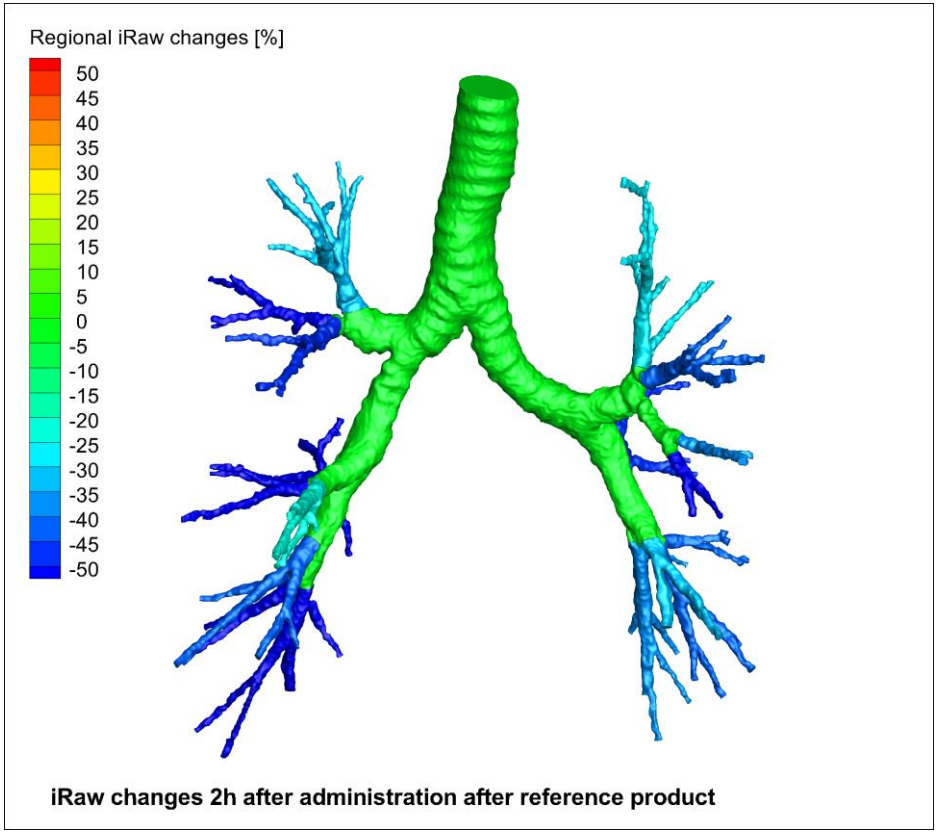
iVaw changes 2h after administration after reference product

RESULTS

- FRI-based airway resistance (iRaw)



iRaw changes 2h after administration after test product

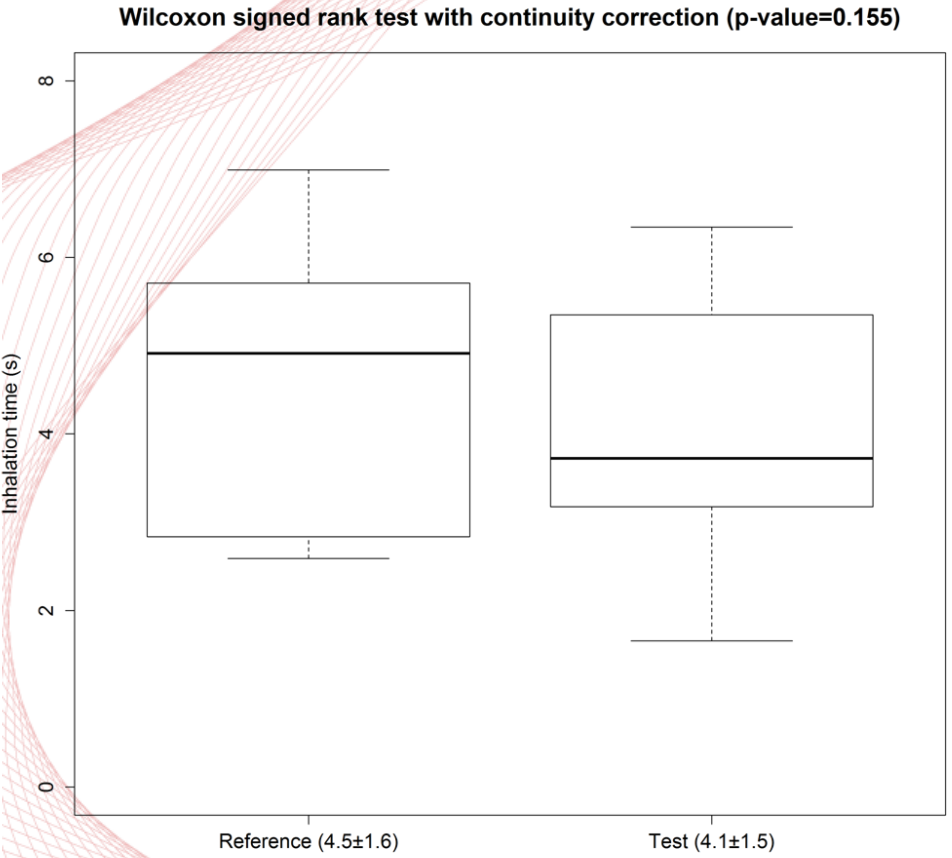


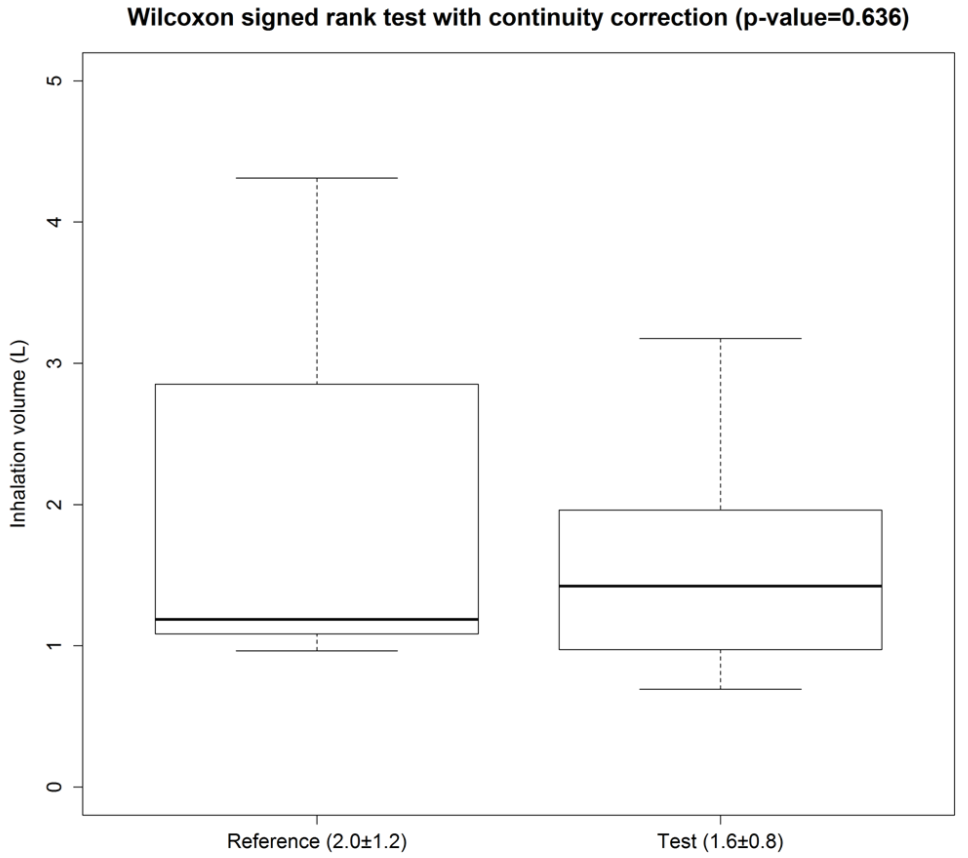
iRaw changes 2h after administration after reference product

FLUIDDA

RESULTS

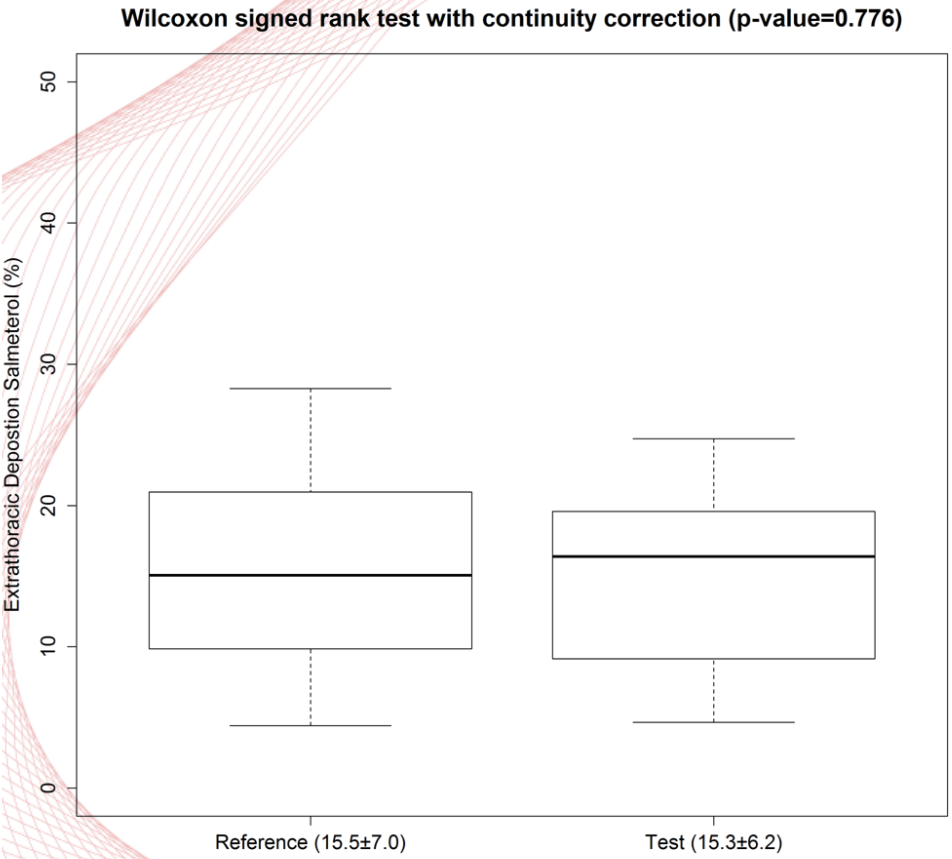
- Inhalation maneuver

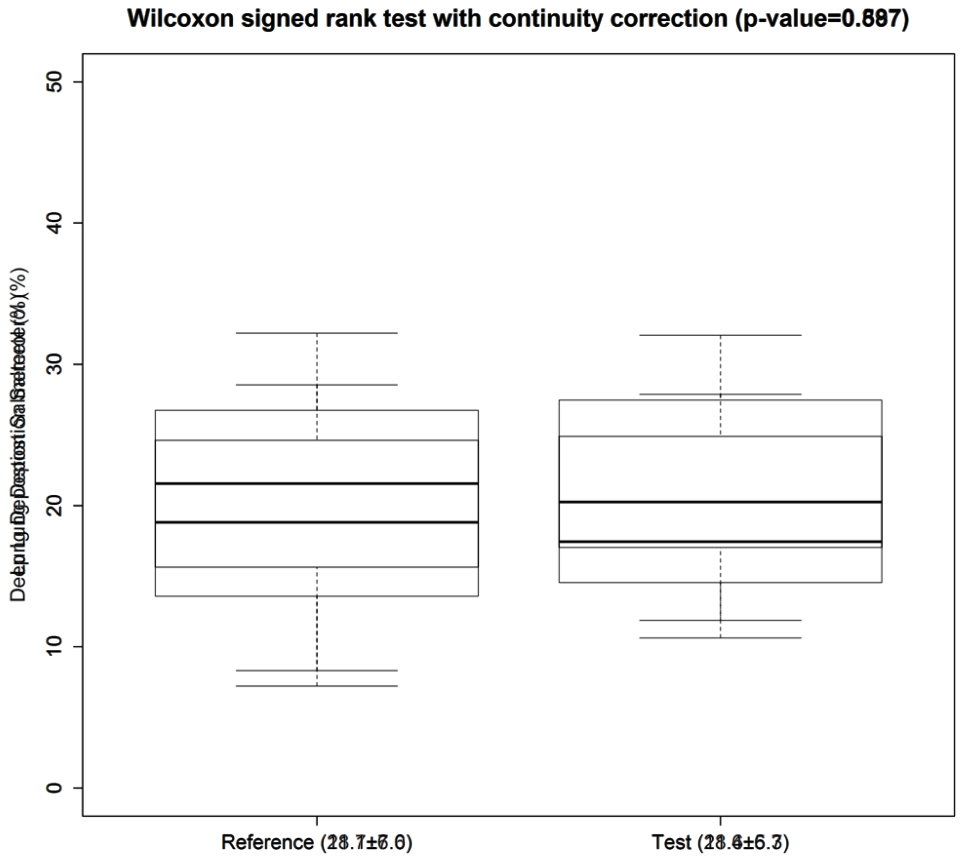




RESULTS

- Drug deposition

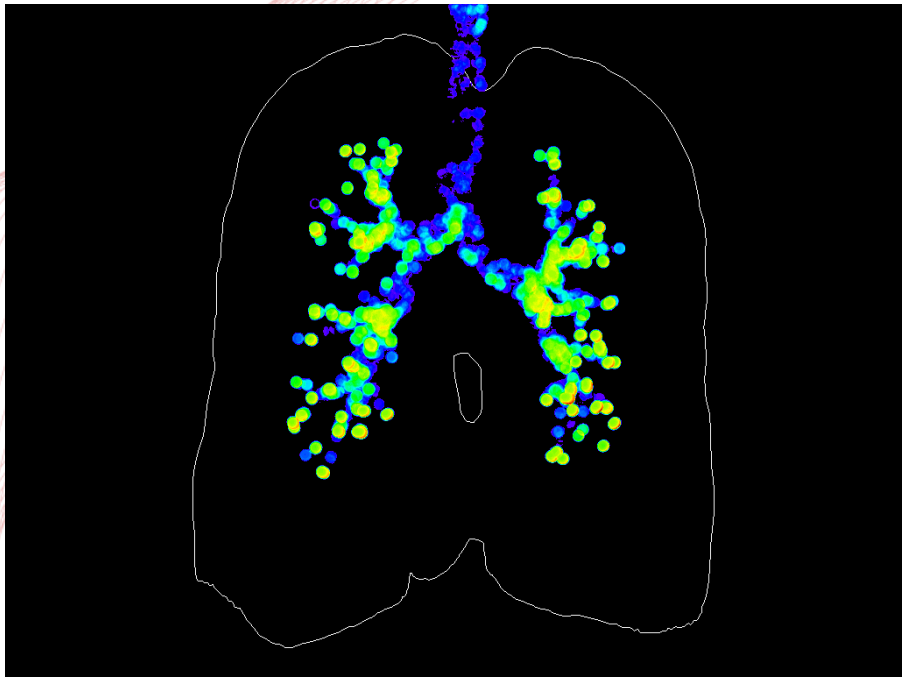




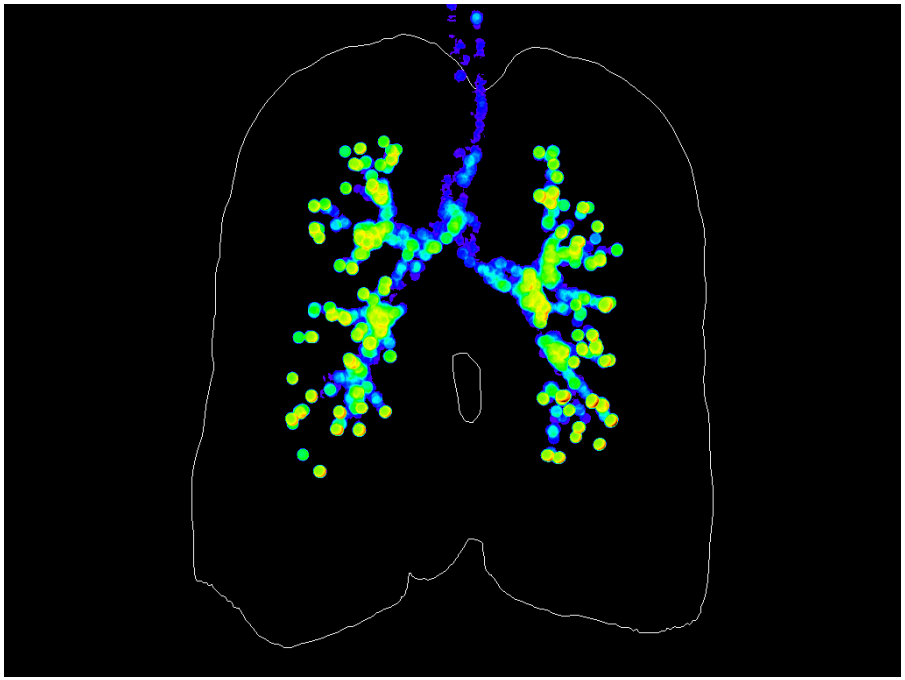
FLUIDDA

RESULTS

- FRI-based aerosol deposition



test

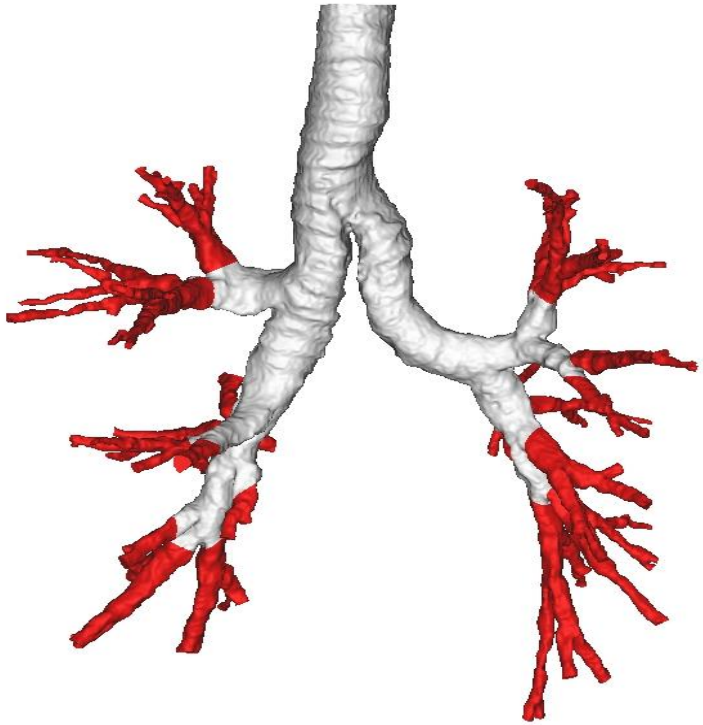


reference

RESULTS

- FRI parameters: drug effect

IMAGING TESTS		Pre Test		Post Test		p-value
		Mean	SD	Mean	SD	
iVaw [cm³]	Total	51.93	23.59	55.66	25.85	0.00048
	Central	40.36	18.26	41.74	19.26	0.00176
	Distal	11.58	6.23	13.91	7.61	0.00048
iSaw [cm²]	Total	290.24	93.13	312.57	103.03	0.00048
	Central	128.03	32.93	131.26	33.92	0.00058
	Distal	162.22	65.29	181.32	74.42	0.00048
iRaw [kPas/L]	Total	0.040	0.024	0.028	0.016	0.00147
	Central	0.014	0.009	0.012	0.007	0.01215
	Distal	0.026	0.017	0.017	0.011	0.00123



FLUIDDA

RESULTS

- FRI parameters: drug comparison

IMAGING TESTS		Pre Test		Pre Reference		p-value	Change Test		Change Reference		p-value
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
iVaw [cm³]	Total	52.59	24.10	51.93	23.59	0.14060	3.72	3.36	3.23	1.82	0.39360
	Central	40.72	18.92	40.36	18.26	0.28910	1.39	1.61	1.03	1.17	0.26630
	Distal	11.87	6.04	11.58	6.23	0.18730	2.34	2.12	2.20	1.37	0.69820
iSaw [cm²]	Total	295.50	89.34	290.24	93.13	0.17060	22.33	17.37	20.25	12.02	0.66030
	Central	129.95	34.29	128.03	32.93	0.28910	3.23	2.68	2.92	3.12	0.33880
	Distal	165.55	60.75	162.22	65.29	0.17060	19.10	15.73	17.32	12.00	0.58720
iRaw [kPas/L]	Total	0.039	0.023	0.040	0.024	0.45340	-0.012	0.013	-0.014	0.013	0.45340
	Central	0.013	0.010	0.014	0.009	0.36550	-0.002	0.003	-0.002	0.003	0.89710
	Distal	0.026	0.017	0.026	0.017	0.77610	-0.010	0.011	-0.012	0.011	0.48510

FLUIDDA

RESULTS

- Clinical parameters: drug effect

CLINICAL TESTS	Pre Test		Post Test		p-value	Pre Reference		Post Reference		p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
FVC [L]	4.20	1.27	4.21	1.28	0.82020	4.21	1.40	4.31	1.46	0.15550
FVC [%p]	120.03	15.48	120.30	14.83	0.77610	119.49	16.88	121.87	15.77	0.28910
FEV1 [L]	2.91	0.96	3.04	0.96	0.00058	2.92	1.03	3.09	1.03	0.00058
FEV1 [%p]	102.32	21.10	106.78	19.98	0.00058	102.01	21.74	108.01	20.16	0.00058
FEV1/FVC [%]	69.71	10.09	72.76	10.25	0.00123	69.69	9.62	72.79	10.41	0.00048
PEF [L/s]	7.90	2.76	8.15	2.68	0.01212	7.94	2.93	8.26	2.75	0.02137
MEF50 [L/s]	2.55	1.27	2.96	1.32	0.00085	2.62	1.24	2.97	1.31	0.00103
FEF75 [L/s]	0.68	0.30	0.82	0.42	0.00102	0.69	0.34	0.88	0.48	0.00287
FEF25 [L/s]	5.22	2.10	5.94	2.03	0.00058	5.26	2.15	6.01	2.42	0.00348
RV [L]	2.58	0.84	2.44	0.74	0.02613	2.59	0.86	2.48	0.70	0.17870
RV [%p]	120.25	28.94	113.88	26.25	0.01832	120.06	28.61	115.63	23.04	0.21440
TLC [L]	6.83	1.85	6.73	1.82	0.01507	6.86	1.93	6.85	1.94	1.00000
TLC [%p]	114.19	13.74	112.69	13.63	0.02273	114.75	14.19	114.56	14.41	0.81300
FRC [L]	3.61	1.13	3.40	1.03	0.00270	3.57	1.09	3.38	0.96	0.00209
FRC [%p]	114.94	24.79	108.25	22.85	0.00234	113.69	23.10	107.69	20.29	0.00264
R [kPas/l]	0.36	0.15	0.28	0.12	0.00270	0.39	0.19	0.25	0.09	0.00048
sR [kPas]	1.43	0.89	1.08	0.66	0.00103	1.54	1.01	0.94	0.46	0.00048
6MWT [m]	636.67	61.09	631.93	62.96	0.21080	626.73	57.29	631.20	62.45	0.20850
6MWT [%p]	98.00	11.67	97.20	12.26	0.23480	96.40	10.13	96.93	10.15	0.46400
SaO2 [%]	97.21	1.25	96.86	1.41	0.32750	96.64	1.95	96.86	1.41	1.00000
SaO2_low [%]	94.43	3.69	93.79	4.64	0.21220	93.50	5.26	93.29	5.38	0.71980
Borg_Dyspnea [0-10] pre 6MWT	0.63	0.97	0.28	0.34	0.12500	0.80	0.94	0.41	0.47	0.02225
Borg_Dyspnea [0-10] post 6MWT	2.34	2.28	1.53	1.63	0.03333	2.40	2.20	1.89	2.07	0.38710

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RESULTS

- Clinical parameters: drug comparison

CLINICAL TESTS	Pre Test		Pre Reference		p-value	Change Test		Change Reference		p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
FVC [L]	4.21	1.40	4.20	1.27	0.90950	0.02	0.18	0.10	0.26	0.16390
FVC [%p]	119.49	16.88	120.03	15.48	0.93820	0.28	5.13	2.38	6.53	0.14050
FEV1 [L]	2.92	1.03	2.91	0.96	1.00000	0.13	0.13	0.18	0.13	0.23290
FEV1 [%p]	102.01	21.74	102.32	21.10	0.79590	4.46	4.01	5.99	4.04	0.29340
FEV1/FVC [%]	69.69	9.62	69.71	10.09	0.97730	3.05	2.43	3.10	1.77	1.00000
PEF [L/s]	7.94	2.93	7.90	2.76	0.73680	0.26	0.39	0.32	0.51	0.58720
MEF50 [L/s]	2.62	1.24	2.55	1.27	0.55090	0.41	0.24	0.35	0.33	0.28910
FEF75 [L/s]	0.69	0.34	0.68	0.30	0.60900	0.15	0.16	0.19	0.21	0.24430
FEF25 [L/s]	5.26	2.15	5.22	2.10	0.55200	0.72	0.47	0.74	0.87	0.85640
RV [L]	2.59	0.86	2.58	0.84	0.95880	-0.14	0.20	-0.11	0.27	0.50140
RV [%p]	120.06	28.61	120.25	28.94	1.00000	-6.38	8.52	-4.44	11.77	0.46850
TLC [L]	6.86	1.93	6.83	1.85	0.45330	-0.10	0.13	-0.01	0.17	0.13940
TLC [%p]	114.75	14.19	114.19	13.74	0.54790	-1.50	2.19	-0.19	3.04	0.23210
FRC [L]	3.57	1.09	3.61	1.13	0.53200	-0.21	0.21	-0.20	0.22	0.81590
FRC [%p]	113.69	23.10	114.94	24.79	0.38150	-6.69	6.26	-6.00	6.30	0.73600
R [kPas/l]	0.39	0.19	0.36	0.15	0.23410	-0.07	0.08	-0.14	0.11	0.06636
sR [kPas]	1.54	1.01	1.43	0.89	0.35190	-0.35	0.40	-0.59	0.59	0.08323
6MWT [m]	626.73	57.29	636.67	61.09	0.18410	-4.73	17.02	4.47	11.13	0.05693
6MWT [%p]	96.40	10.13	98.00	11.67	0.16830	-0.80	2.46	0.53	1.92	0.15010
SaO2 [%]	96.64	1.95	97.21	1.25	0.14630	-0.36	1.28	0.21	1.81	0.35070
SaO2_low [%]	93.50	5.26	94.43	3.69	0.23460	-0.64	1.78	-0.21	1.81	0.32370
Borg_Dyspnea [0-10] pre 6MWT	0.80	0.94	0.63	0.97	0.73490	-0.34	0.78	-0.37	0.50	0.67400
Borg_Dyspnea [0-10] post 6MWT	2.40	2.20	2.34	2.28	0.96870	-0.81	1.26	-0.51	1.45	0.34930

FLUIDDA

RESULTS

- Clinical parameters: drug comparison

CLINICAL TESTS	Pre Test		Pre Reference		p-value	Change Test		Change Reference		p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
FVC [L]	4.21	1.40	4.20	1.27	0.90950	0.02	0.18	0.10	0.26	0.16390
FVC [%p]	119.49	16.88	120.03	15.48	0.93820	0.28	5.13	2.38	6.53	0.14050
FEV1 [L]	2.92	1.03	2.91	0.96	1.00000	0.13	0.13	0.18	0.13	0.23290
FEV1 [%p]	102.01	21.74	102.32	21.10	0.79590	4.46	4.01	5.99	4.04	0.29340
FEV1/FVC [%]	69.69	9.62	69.71	10.09	0.97730	3.05	2.43	3.10	1.77	1.00000
PEF [L/s]	7.94	2.93	7.90	2.76	0.73680	0.26	0.39	0.32	0.51	0.58720
MEF50 [L/s]	2.62	1.24	2.55	1.27	0.55090	0.41	0.24	0.35	0.33	0.28910
FEF75 [L/s]	0.69	0.34	0.68	0.30	0.60900	0.15	0.16	0.19	0.21	0.24430
FEF25 [L/s]	5.26	2.15	5.22	2.10	0.55200	0.72	0.47	0.74	0.87	0.85640
RV [L]	2.59	0.86	2.58	0.84	0.95880	-0.14	0.20	-0.11	0.27	0.50140
RV [%p]	120.06	28.61	120.25	28.94	1.00000	-6.38	8.52	-4.44	11.77	0.46850
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TLC [%p]	114.75	14.19	114.19	13.74	0.54790	-1.50	2.19	-0.19	3.04	0.23210
FRC [L]	3.57	1.09	3.61	1.13	0.53200	-0.21	0.21	-0.20	0.22	0.81590
FRC [%p]	113.69	23.10	114.94	24.79	0.38150	-6.69	6.26	-6.00	6.30	0.73600
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sR [kPas]	1.54	1.01	1.43	0.89	0.35190	-0.35	0.40	-0.59	0.59	0.08323
6MWT [m]	626.73	57.29	636.67	61.09	0.18410	-4.73	17.02	4.47	11.13	0.05693
6MWT [%p]	96.40	10.13	98.00	11.67	0.16830	-0.80	2.46	0.53	1.92	0.15010
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Borg_Dyspnea [0-10] pre 6MWT	0.80	0.94	0.63	0.97	0.73490	-0.34	0.78	-0.37	0.50	0.67400
Borg_Dyspnea [0-10] post 6MWT	2.40	2.20	2.34	2.28	0.96870	-0.81	1.26	-0.51	1.45	0.34930

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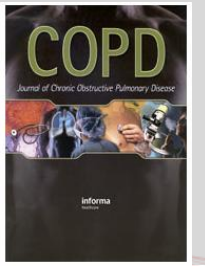
RESULTS

- Seretide FS and Cipla FS are not significantly different
- Are they equivalent?
  - Transform parameters to normal distributions (when needed)
  - Determine 90% CI
  - Assess whether 90% CI lies within 80%-125% bounds
    - Case 1: Atrovent vs Ventolin
    - Case 2: Seretide FS vs Cipla FS

ATROVENT vs VENTOLIN

- Assess acute effect of **Salbutamol** (Ventolin) in comparison with **Ipratropium Bomide** (Atrovent)
- Prospective cross over study
- 6 COPD patients
- 400 microgram Ipratropium Bromide / 80 microgram Salbutamol
- Are these products equivalent according to different parameters?



De Backer LA, Vos WG, De Backer JW, Devolder A, Verhulst SL, Claes R, Salgado R, Germonpré PR, De Backer WA

The effect of salbutamol in comparison with ipratropium bromide on central and peripheral airways in COPD

Int J Chron Obstruct Pulmon Dis. 2011;6:637-46.

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ATROVENT vs VENTOLIN

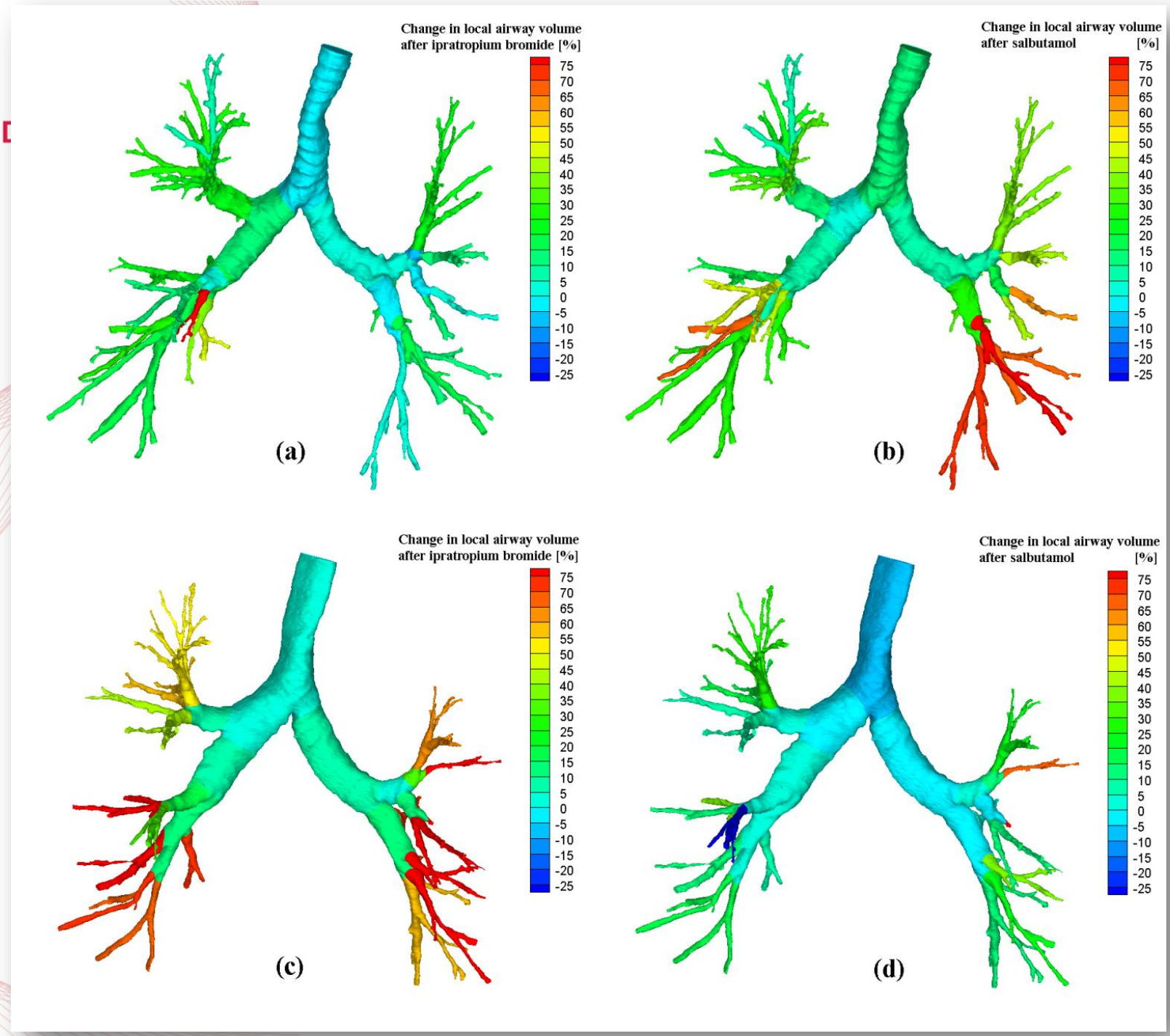
Table 3 Lung function changes after salbutamol and ipratropium bromide

Patient number	ΔFEV_1 (% pred)	ΔFEV_1 (% pred)	ΔVC (L)	ΔVC (L)	ΔR (kPa/L)	ΔR (kPa/L)	$\Delta specR$ (kPa)	$\Delta specR$ (kPa)				
Lung function testing												
1	4	6	0.22	0.37	−0.120	−0.260	−1.44	−1.59				
2	0	1	0.23	−0.01	−0.161	0.089	−1.00	0.19				
3	6	4	0.28	0.27	−0.479	−0.201	−2.06	−0.91				
4	8	6	0.55	0.54	−0.560	−0.461	−4.46	−3.38				
5	3	6	0.04	0.20	−0.171	−0.339	−0.89	−1.51				
Average	4.2	3.6	0.26	0.27	−0.298	−0.234	−1.97	−1.44				
	ΔV_{tot} (%)	ΔV_{tot} (%)	ΔV_{cent} (%)	ΔV_{cent} (%)	ΔV_{dist} (%)	ΔV_{dist} (%)	ΔR_{awtot} (%)	ΔR_{awtot} (%)	ΔR_{awcent} (%)	ΔR_{awcent} (%)	ΔR_{dist} (%)	ΔR_{dist} (%)
Functional imaging												
1	18.1	8.3	9.9	3.7	38.8	19.9	−44	−19	−30	0	−54	−33
2	11.1	8.0	5.7	5.6	39.9	20.8	−55	−41	−15	−16	−68	−49
3	19.6	10.9	10.0	5.8	80.6	43.7	−63	−56	−8	−13	−82	−71
4	0.7	17.6	−3.0	5.4	15.8	67.5	−27	−64	24	0	−37	−77
5	9.4	4.5	6.8	0.9	15.9	13.7	−34	−31	−37	−34	−33	−30
Average	10.8	10.5	5.0	4.5	31.6	32.4	−47.6	−44.5	−17.7	−16.7	−57.2	−58.1

Abbreviations: FEV_1, forced expiratory volume in 1 second; VC, vital capacity; R, airway resistance; specR, specific airway resistance (corrected for lung volume R × FRC); V_{tot}, total volume of the segmented airways; V_{centr}, volume of the central airways until the third bifurcation; V_{dist}, volume of the distal airways from third to seventh bifurcation; R_{awtot}, airway resistance of all segmented airways; $R_{awcentr}$, airway resistance on the central airways until the third bifurcation; R_{awdist}, airway resistance of the distal airways from third to seventh bifurcation; % pred, percentage predicted.

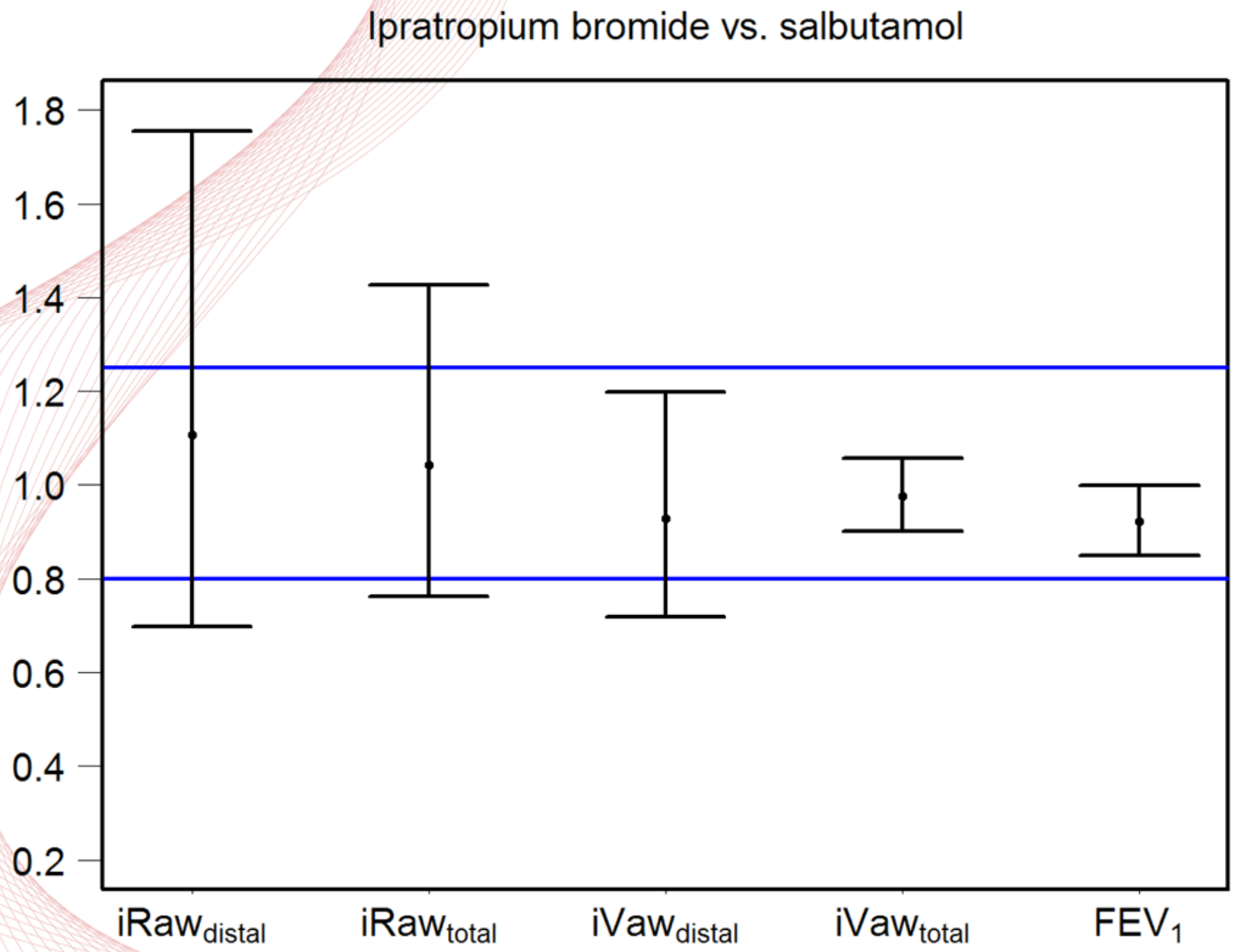
Notes: Grey shading indicates changes after salbutamol; no shading indicates changes after ipratropium bromide.

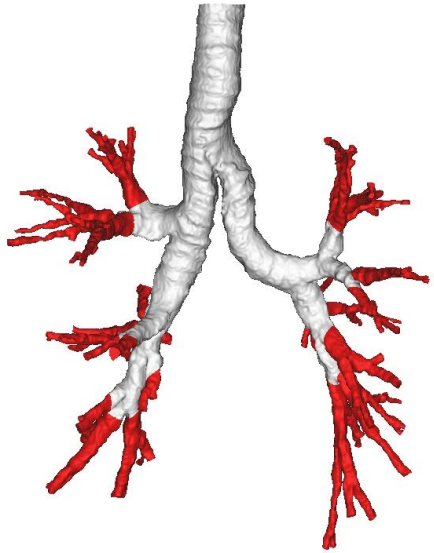
FLUID



Change in local airway volume after ipratropium bromide [%]
75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25
(a)
Change in local airway volume after salbutamol [%]
75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25
(b)
Change in local airway volume after ipratropium bromide [%]
75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25
(c)
Change in local airway volume after salbutamol [%]
75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25
(d)

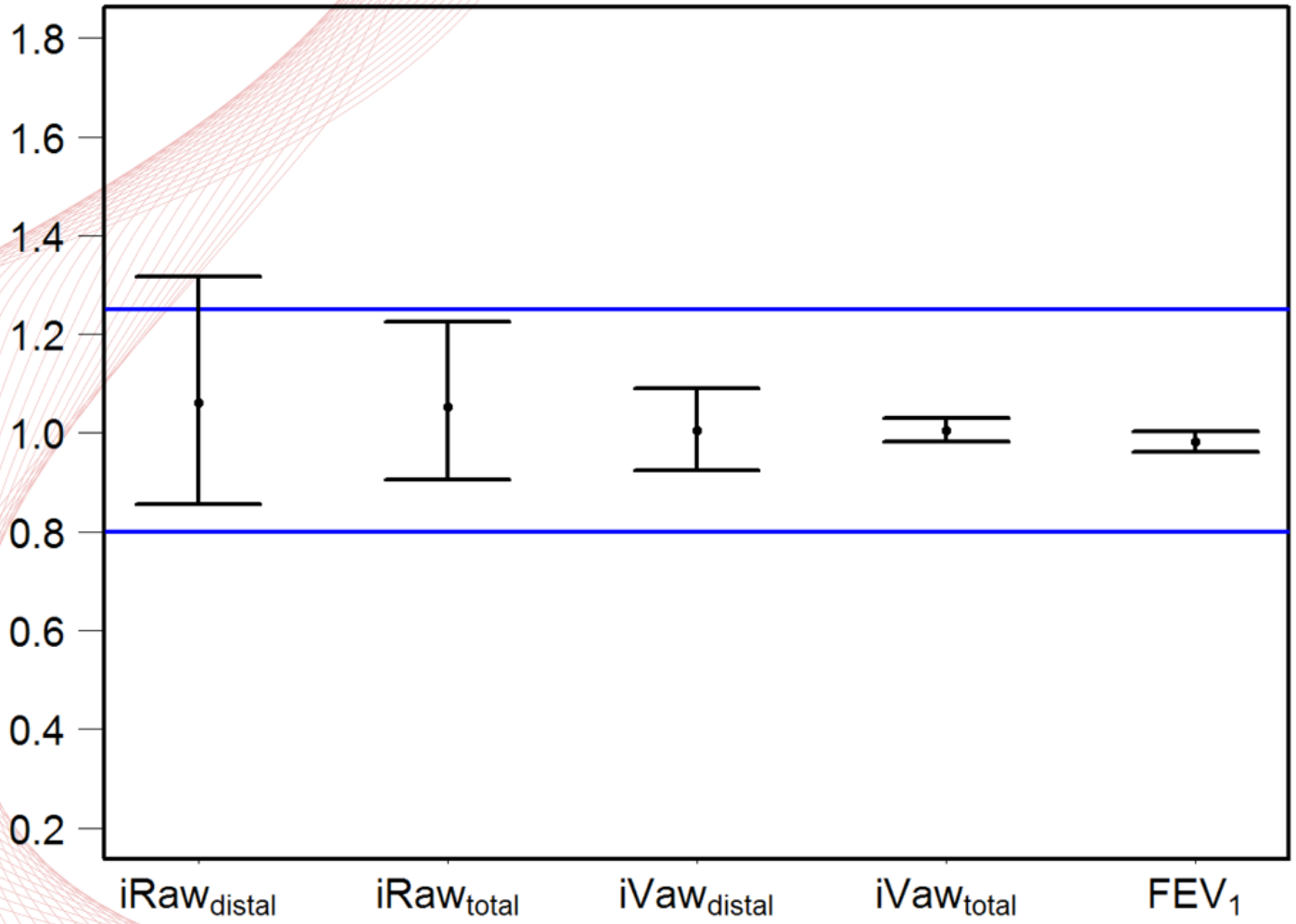
ATROVENT vs VENTOLIN

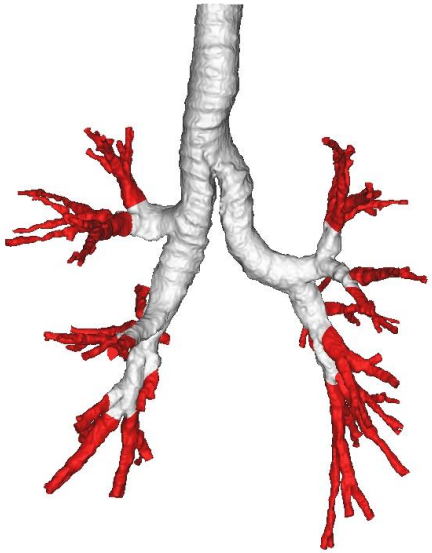




FLUIDDA

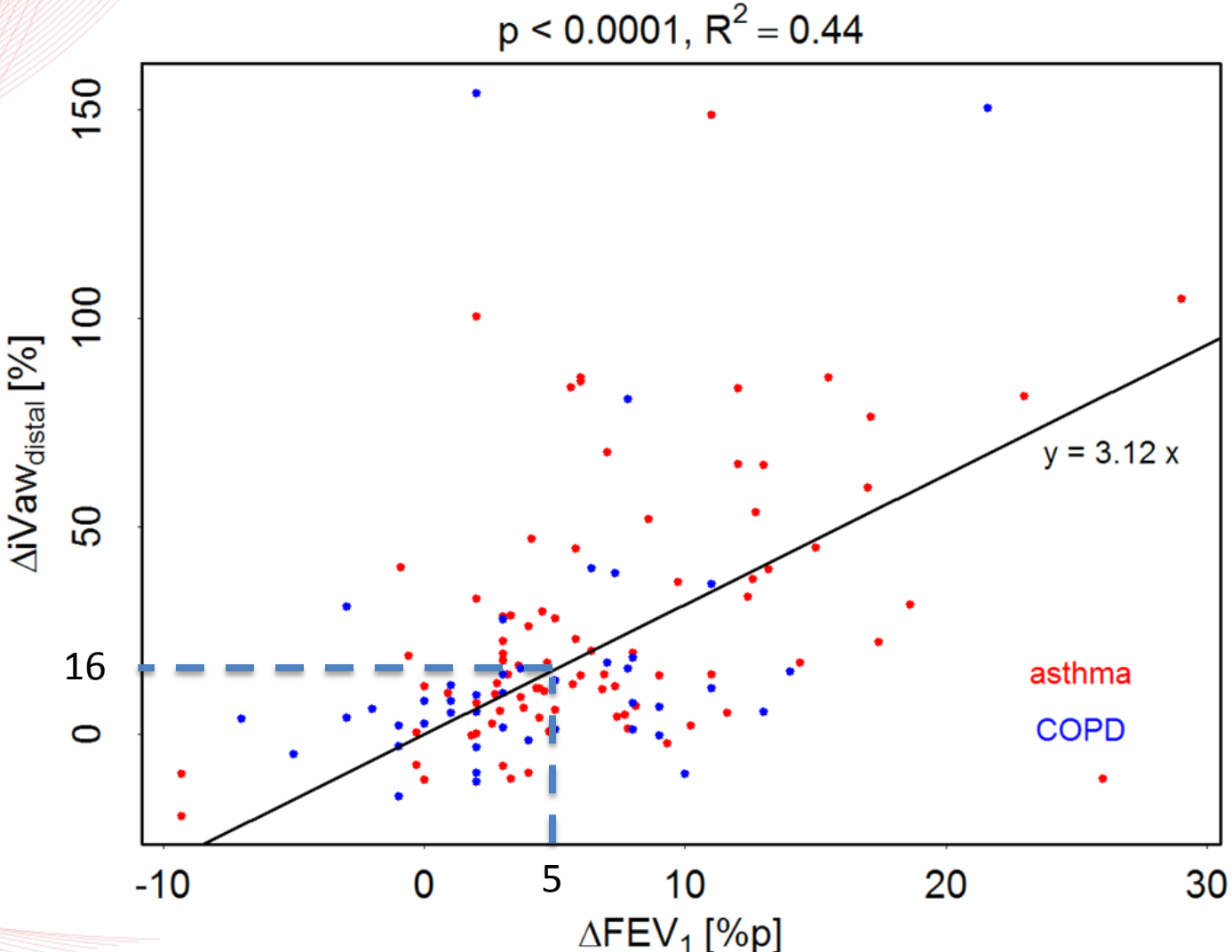
Branded vs. generic salmeterol/fluticasone





CORRELATION BETWEEN GEOMETRY AND QOL

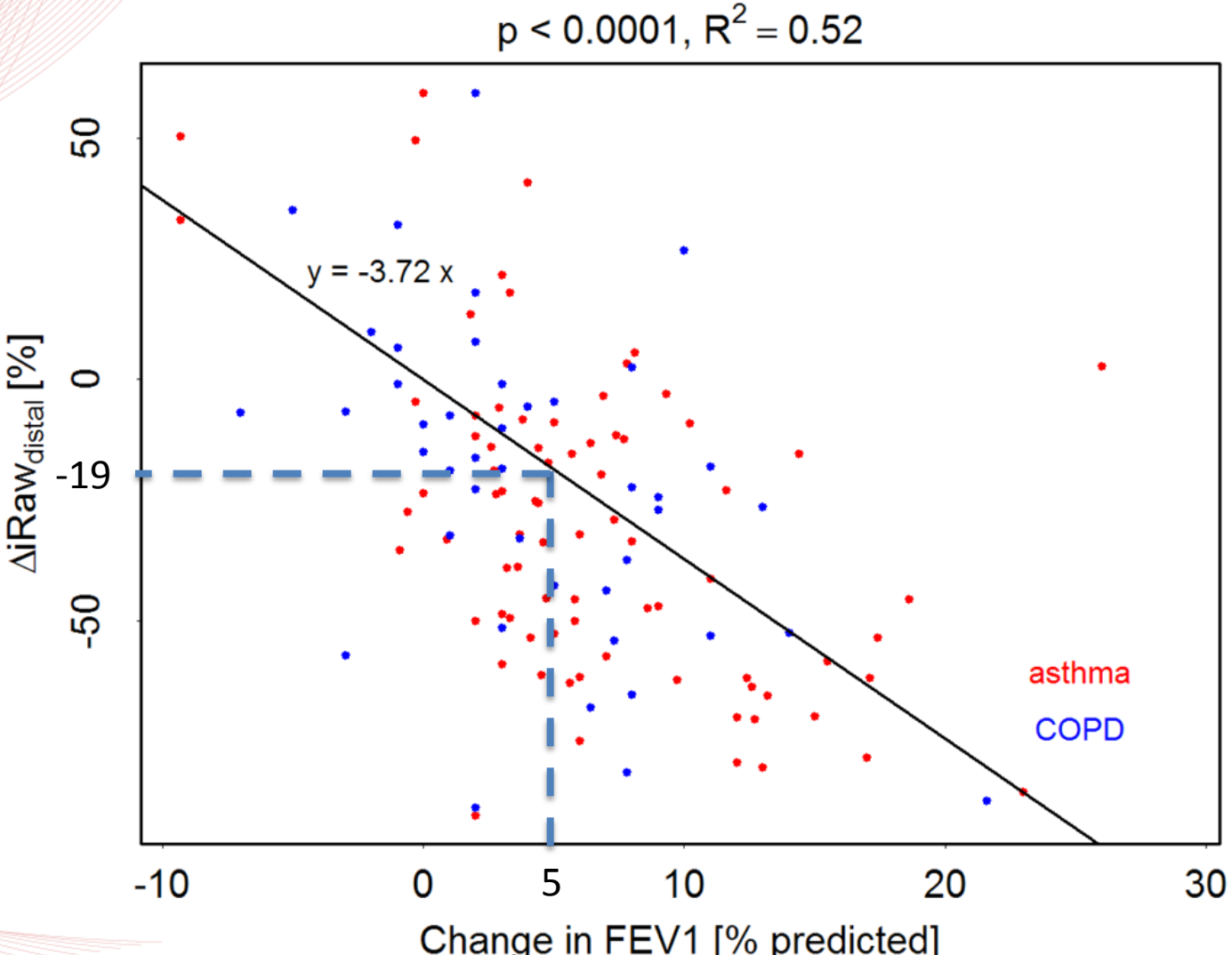
COPD and Asthma Population (pooled data)



Data on file

CORRELATION BETWEEN GEOMETRY AND QOL

COPD and Asthma Population (pooled data)



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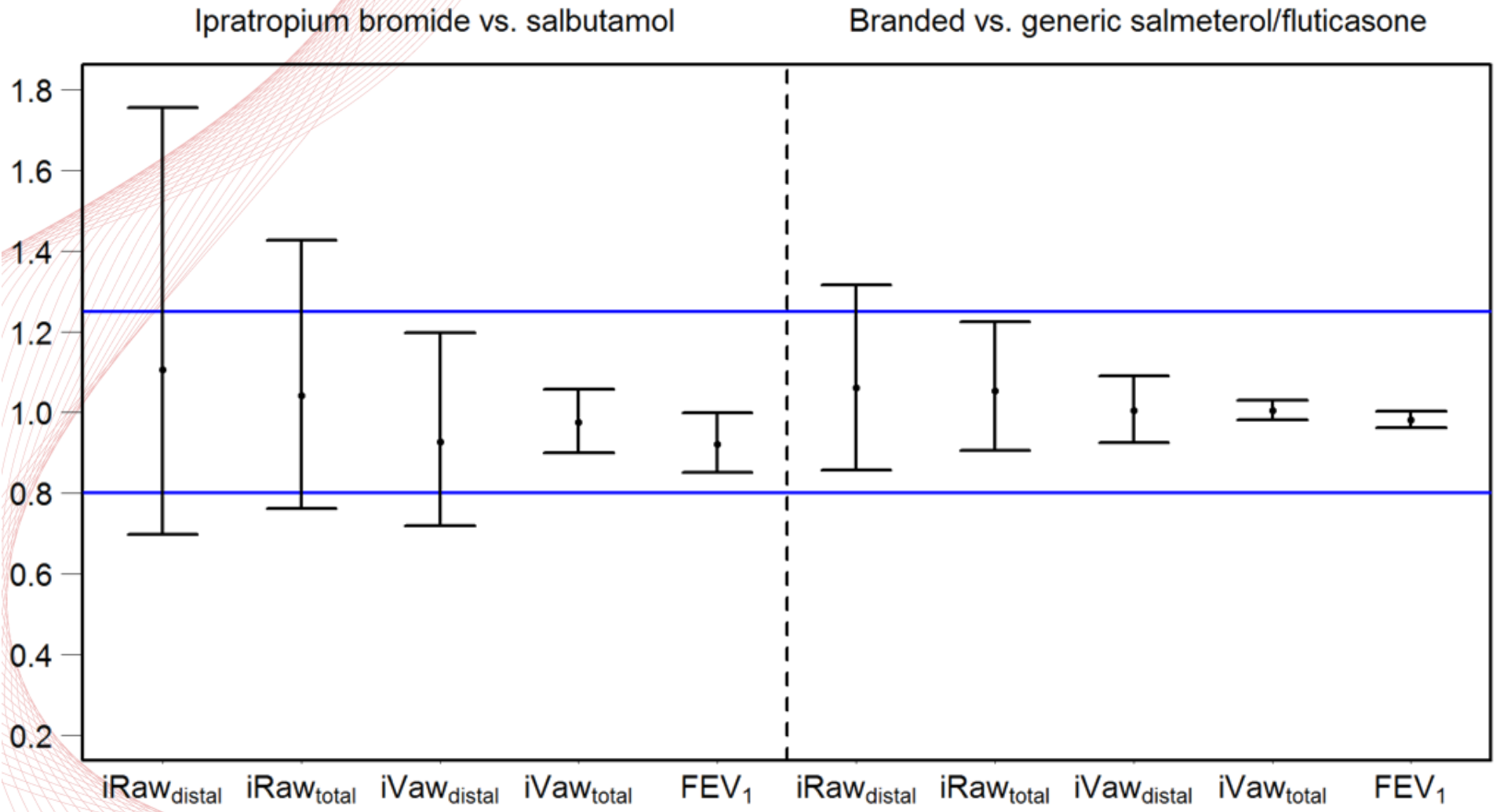
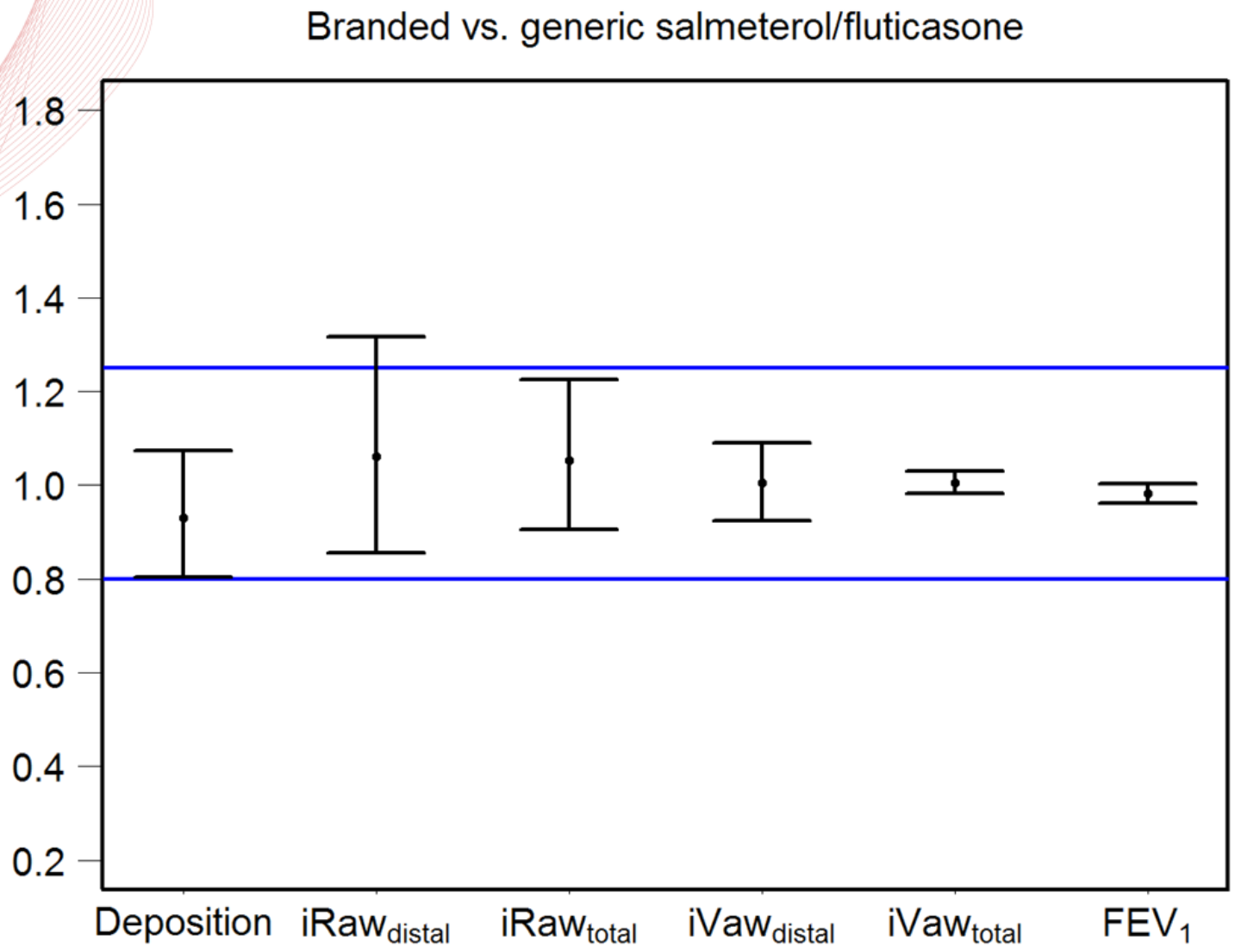
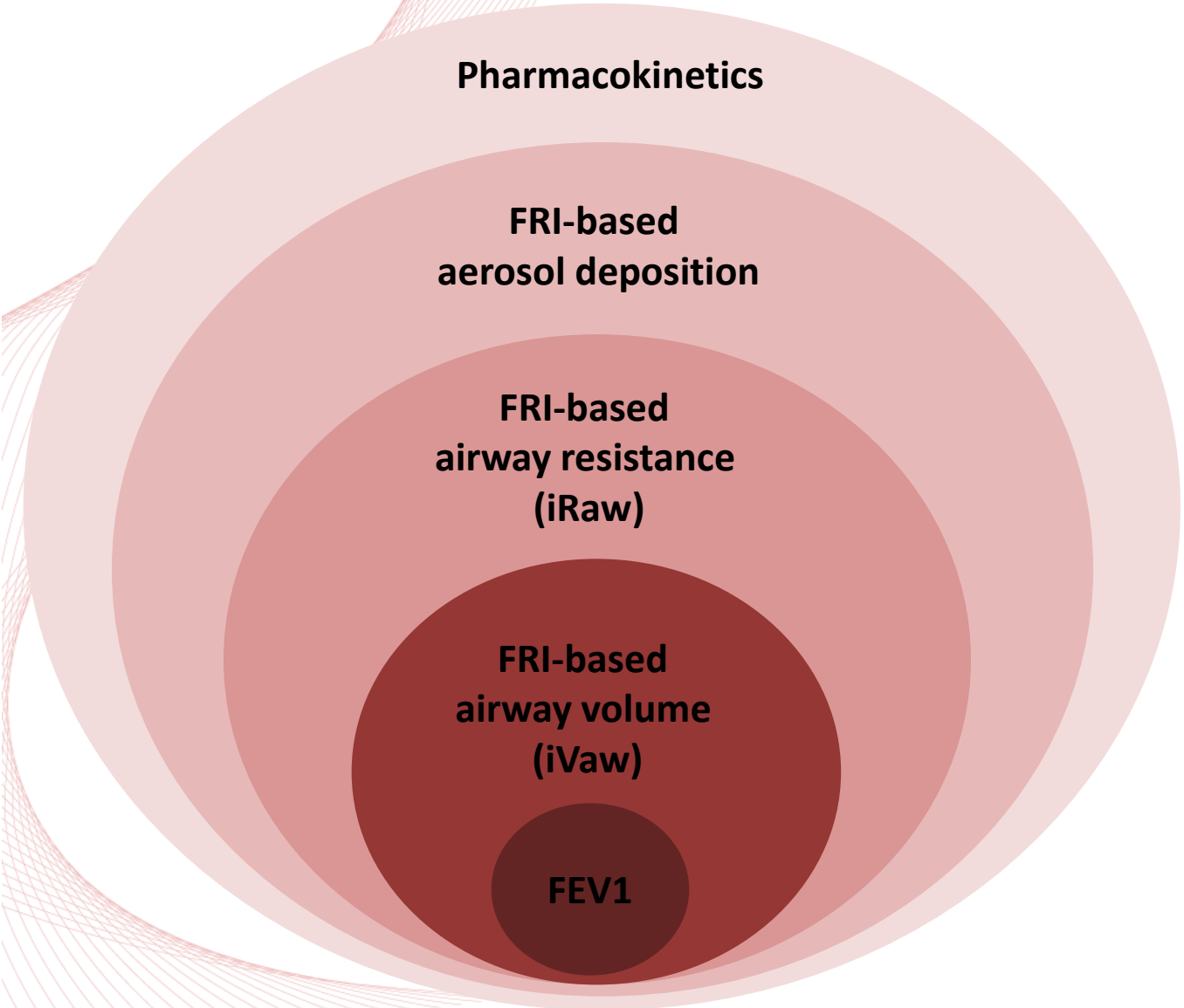

Ipratropium bromide vs. salbutamol
Branded vs. generic salmeterol/fluticasone
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
iRaw distal
iRaw total
iVaw distal
iVaw total
FEV1
iRaw distal
iRaw total
iVaw distal
iVaw total
FEV1

FLUIDDA


Branded vs. generic salmeterol/fluticasone
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
Deposition
iRaw distal
iRaw total
iVaw distal
iVaw total
FEV1

FRI TO BRIDGE BETWEEN PK AND PD



High ability to differentiate products

Low ability to differentiate products

FLUIDDA

CONCLUSIONS

- FRI is more sensitive compared to standard PFT
- FRI can yield regional information in small scale clinical trials
- FRI has the potential to bridge between PK and PD