Supplementary Material

Supplementary Table S1 Physiology of the lung,[17,a,b,c] alveolar surface in acinus, approximate density of receptors[18], smooth muscles, submucosal glands, and ganglia in the lungs: 0: absent, -0: present but very little density. +0: present but density is not known. +…++++: little to high density. The densities of M1, M2, and M3 receptors are an interpretation. For numerical data please refer to the publication by Ikeda et al.[18] Ratio of submucosal glands with kind permission.
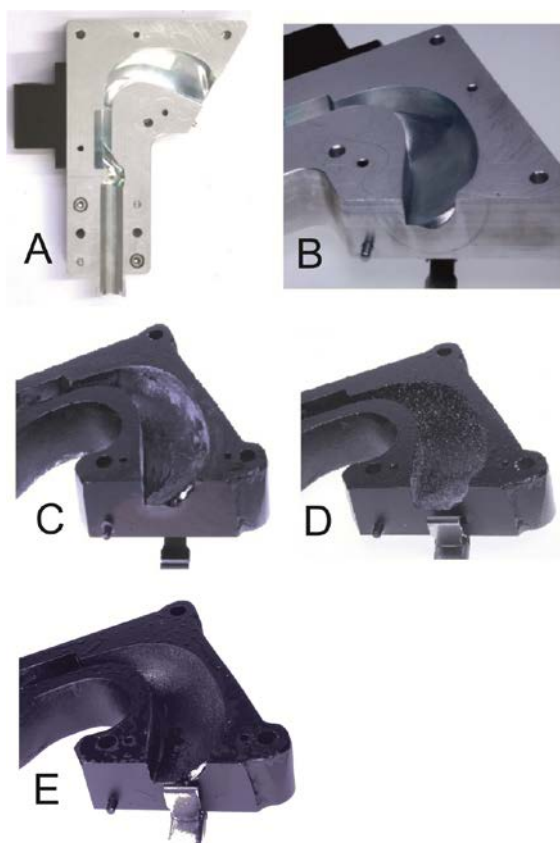
Part of the lung	Airway generation (approx.)	alveolar surface in acinus [mm²] for gas exchange	Density			Smooth muscles M3	submucosal glands[17] M1(36%) M3(64%)	parasympathetic ganglia M1
			M1	M2	M3			
Trachea	0	0	-0	+++	+++	+	+++	+0
Bronchus principalis	1	0	-0	+++	+++	++	+++	+0
Bronchus lobaris	2	0	-0	++	+++	++	++	+0
Bronchus segmentalis	3	0	-0	++	+++	++	++	+0
Bronchus subsegmentalis	4	0	-0	+	++	+++	+	+0
Bronchi	5 to 8	0	-0	+	++	+++	+	+0
Bronchioli	9 to 14	0	+++	++	++	+++	0	+0
Bronchiolus terminalis	15 to 17	Increasing from top to bottom, see ref. [9]	+++	+++	++	++++	0	+0
Bronchiolus respiratorius	18 to 20		+++	+++	++	++++	0	+0
Ductus alveolaris	21 to 23		+++	+++	+	++	0	+0
Sacculus alveolaris	24		+++	+++	+	0	0	+0

Further references:

a.   Junqueira LC, Carneiro J. Respiratory System. *Histology*. 6 ed 2004:287.
b.   Schiebler TH. Respiratory System. *Anatomy*. 8 ed 1999:498.
c.   Lammers J, Minette P, McCuster M, Barnes PJ. The Role of Pirenzepine-sensitive (M1) Muscarinic Receptors in vagally Mediated Bronchoconstriction in Humans. *American Review of Respiratory Disease.* 1989;139:446-449.

Supplementary Table S2 Lung geometry according to Finlay et al,[1] angles were chosen from the work of Raabe et al, male,[8] the cusp curvature radius was approx. 10% of the parent-branch diameter. With kind permission.

Generation	length [cm]	diameter [cm]	cum. Volume (incl. Alveoli) [cm³]	angle between daughter-branches [°]	cusp curvature radius [mm]
0	12.456	1.81	32.05	40	1.81
1	3.614	1.414	43.40	25	1.41
2	2.862	1.115	54.57	45	1.22
3	2.281	0.885	65.79	20	0.83
4	1.78	0.706	76.92	30	0.75
5	1.126	0.565	85.95	60	0.60
6	0.897	0.454	95.24	25	0.42
7	0.828	0.364	106.24	40	0.36
8	0.745	0.286	118.46	40	0.29
9	0.653	0.218	130.92	35	0.22
10	0.555	0.162	142.71	25	0.16
11	0.454	0.121	153.38	45	0.12
12	0.357	0.092	163.12	60	0.092
13	0.277	0.073	172.64	40	0.073
14	0.219	0.061	183.13	45	0.061
15	0.134	0.049	204.97	60	0.049
16	0.109	0.048	239.90	50	0.048
17	0.091	0.039	284.10	30	0.039
18	0.081	0.037	357.89	75	0.037
19	0.068	0.035	474.05	60	0.035
20	0.068	0.033	689.87	30	0.033
21	0.068	0.03	1067.71	50	0.030
22	0.065	0.028	1742.74	50	0.028
23	0.073	0.024	3000	50	-

Supplementary Figure S1 Deposition in the throat models, for better visibility 10 inhalations (moderate COPD) were accumulated and the models were opened.

A) Total view on the model.
B) 0.5% methylene blue solution administered by Respimat (tiotropium solution would have been transparent and invisible).
C) Seebri formulation administered by Breezhaler.
D) Eklira formulation administered by Genuair inhaler.
E) Relvar formulation administered by Ellipta inhaler
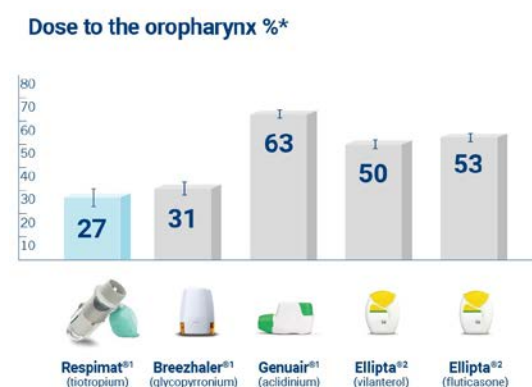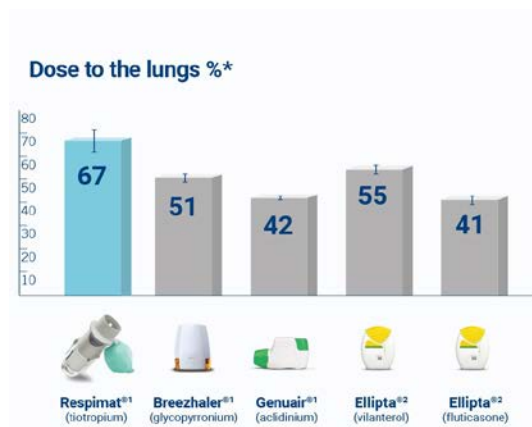
Supplementary Figure S2 In vitro data on the dose to the lungs (mDTL) was acquired using the idealized Alberta throat model and averaged breathing patterns of very severe COPD patients (matched to the flow resistance of the devices) to compare Respimat, Breezhaler, Genuair and Ellipta. * Dose obtained in-vitro and related to label claim of the respective inhaler.

Supplementary Figure S3

Summary results of the combined in-vitro and CFD study, values given as %ND:

A) laminar flow. B) turbulent flow. Experimental data is given for throat deposition and mDTL. CFD simulation data presenting groupings of the following airway generations: Trachea-G4, G5-G14, G15-20, G21-alveoles. In the main section G15-alveoles are pooled. Missing or spare percentages of drug ND are due to inhaler deposition and drug recovery being below or above 100% of the ND.