

Table 1 Summary of studies for fluticasone propionate and budesonide<sup>#</sup>

Drug / substance	Study No	Description	Population	Device	Dose [µg]	Comment	References
Gold / polystyrene	1	Insoluble mono-disperse particle	Healthy volunteers	“compressed air nebulizer”	NA	Insoluble particles to evaluate mucociliary clearance model	Smith et al. (1)
Fluticasone propionate	2	Mono-disperse particles	Asthma patients	Spinning top aerosol generator	50	Included to allow direct comparison between different inhaled particle sizes	Usmani et al. (2, 3)
	3	Sandoz Citizen Petition	Healthy volunteers	Diskus®	100, 250, 500 (in combination with 50 µg Salmeterol)	Geometric mean data of 31 individual batches	Chrystyn (5), Tarsin et al. (6), Kamin et al. (4), Sandoz Citizen Petition (7)
	4	PK study	Healthy volunteers	Diskus®	200, 500 µg (Single dose and steady state)	Study, which simultaneously provides budesonide and fluticasone propionate data	Möllmann et al. (8)
	5	PK study (IV + inhaled)	Healthy volunteers and COPD patients	pMDI + spacer	1000 µg (both iv + inhaled)		Singh et al. (9)
	6	PK study	Healthy volunteers and moderately severe asthmatics	Accuhaler®	1000 µg	Clear difference between healthies and asthmatics	Harrison and Tattersfield (10)
	7	IV PK study	Healthy volunteers	NA	250, 500, 1000 µg		Mackie et al. (11)
	8	PK study (IV + inhaled)	Healthy volunteers and mild asthmatic patients	Diskus®, pMDI	1000 µg (200 µg IV)	Publication demonstrates that systemic disposition is not different in healthies and asthmatics	Thorsson et al. (12)
	9	PK study (IV + inhaled)	Healthy volunteers	Diskhaler®, Diskus®	1000 µg (250 µg IV)		Mackie et al. (13)
	10	PK study (inhaled)	Mild-to-moderate asthmatic patients		100 / 500 µg Diskhaler, 500 µg Diskus®		Falcoz et al. (14)
	11	IV PK study	Healthy volunteers and asthmatic patients	NA	Not provided	Even though asthma and healthy data is available; no difference was investigated	Källen and Thorsson (15)
	Budesonide	4	PK in healthy volunteers	Healthy volunteers	Turbohaler®	400, 1000 µg (Single dose and steady state)	Study, which simultaneously provides budesonide and fluticasone propionate data

6	PK study	Healthy volunteers and moderately severe asthmatics	Turbohaler®	1200 µg	No relevant difference between healthies and asthmatics	Harrison and Tattersfield (10)
8	PK study (IV + inhaled)	Healthy volunteers and (mild) asthmatic patients	Turbohaler®	1000 µg (200 µg IV)	Publication demonstrates that systemic disposition is not different in healthies and asthmatics	Thorsson et al. (12)
12	PK study (IV + inhaled)	Healthy volunteers	Turbohaler, pMDI	1000 µg		Thorsson et al. (16)
11	IV PK study	Healthy volunteers and asthmatic patients	NA	Not provided	Even though asthma and healthy data is available; no difference was investigated	Källén and Thorsson (15)

IV: intravenous, NA: not applicable, PK: pharmacokinetics, pMDI: pressurized metered dose inhaler

\* The deposition patterns, which were initially calculated for healthy volunteers based on the MPPD tool, were adapted based on the central/ intermediate to peripheral deposition ratios reported by Usmani et al. for asthmatic patients. FP: Fluticasone propionate, TED: total emitted dose (as % of total nominal dose)

# Green-shaded studies were investigated for model evaluation. Study 1 for evaluation of the deposition and mucociliary clearance model of the overall simulation framework, Study 2 to evaluate the pharmacokinetics after inhalation of different particle sizes with varying aerodynamic particle size, Study 4 to evaluate the predicted pharmacokinetics between budesonide and fluticasone propionate, and Study 6 to compare the predicted pharmacokinetics for both healthy volunteers and asthmatics. Other studies were not considered, as these did not include a comparison of one of the above listed aspects within a single study.

Table 2 PK parameters reported / calculated for the PK studies provided in Table 1

Drug / substance	Study No	Description	PK Parameters	Cmax		tmax [min]	AUC		Comments	References
				Reported Cmax	Dose-normalized Cmax [nmol/L / mg dose]		Reported AUC	Dose-normalized AUC [nmol/L*h / mg dose]		
Gold / poly-styrene	1		Profile of particles in the lung over time	Not applicable, gold and styrene particles are mainly not being absorbed						Smith et al. (1)
FP	2	1.5 µm 50 µg	C <sub>max</sub> , t <sub>max</sub> , AUC <sub>0-12h</sub>	425 pg/mL	17.0	8	923 pg/mL*h	36.9	Even with 100% lung dose and 100% pulmonary bioavailability, the AUC is still higher than expected	Usmani et al. (2, 3)
		3 µm 50 µg		278 pg/mL	11.1	19	891 pg/mL*h	35.6		
		6µm 50 µg		85.0 pg/mL	3.40	30	222 pg/mL*h	8.87		
	3		Dose-normalized C <sub>max</sub> , t <sub>max</sub> , geometric mean PK profiles							Chrystyn (5), Tarsin et al. (6), Kamin et al. (4), Sandoz Citizen Petition (7)
	4	200 µg Day 1	C <sub>max</sub> , AUC, mean PK profiles	0.037 ng/mL	0.370	90	0.22 ng/mL*h	2.20		Möllmann et al. (8)
		200 µg Day 5		0.058 ng/mL	0.579	30	0.30 ng/mL*h	3.00		
		500 µg Day 1		0.094 ng/mL	0.376	90	0.79 ng/mL*h	3.16		
		500 µg Day 5		0.156 ng/mL	0.623	90	0.94 ng/mL*h	3.76		
	5	1000 µg Healthy	C <sub>max</sub> , AUC, mean PK profiles	421 pg/mL	0.841	45	2996 pg/mL*h	5.99	FP administered with pMDI	Singh et al. (9)
		1000 µg COPD		235 pg/mL	0.469	45	1961 pg/mL*h	3.92	44% decreased Cmax and 35% decreased AUC compared to healthies	
	6	1000 µg Healthy	Cmax, AUC, mean PK profiles	130 pg/mL	0.260	60-120	712 pg/mL*h	1.42		Harrison and Tattersfield (10)

		1000 µg Asthmatic		78 pg/mL	0.156	60-120	404 pg/mL*h	0.807	40% decreased Cmax and 43% decreased AUC compared to healthies	
	8	1000 µg Healthy	C <sub>max</sub> , AUC, mean PK profiles	0.5 nmol/L	0.5	100	3.5 nmol/L*h	3.5	Complete PK profiles only provided as a summary of healthies and mild asthmatics	Thorsson et al. (12)
		1000 µg Asthmatic		0.4 nmol/L	0.4	79	3.0 nmol/L*h	3.0	Low time points considered as intention to treat (log scale jitter data points?)	
	9	1000 µg Diskus	C <sub>max</sub> , t <sub>max</sub> , AUC, mean PK profiles	0.339 µg/L	0.677	25	2.49 µg/L*h	4.97	20% decreased Cmax and 14% decreased AUC compared to healthies	Mackie et al. (13)
	10	500 µg Diskus Asthmatics	C <sub>max</sub> , t <sub>max</sub> , AUC, mean PK profile at steady state	0.092 µg/L	0.368	40	0.474 µg/L*h	1.89	TBD	Falcoz et al. (14)
Budesonide	4	500 µg Day 1	C <sub>max</sub> , AUC, mean PK profiles	0.45 ng/mL	2.09	10	0.99 ng/mL*h	4.60		Möllmann et al. (8)
		500 µg Day 5		0.48 ng/mL	2.23	30	1.22 ng/mL*h	5.67		
		1000 µg Day 1		0.90 ng/mL	2.09	10	2.53 ng/mL*h	5.88		
		1000 µg Day 5		1.10 ng/mL	2.55	20	2.98 ng/mL*h	6.92		
	6	Healthy 1200 µg	C <sub>max</sub> , AUC, mean PK profiles	2432 pg/mL	4.70	NA	6467 pg/mL*h	12.5	Dose-normalized AUC and Cmax for healthies ~2 fold higher than reported in Möllmann et al. (at a comparable dose)	Harrison and Tattersfield (10)
		Asthmatic 1200 µg		2276 pg/mL	4.40	NA (first time point already t <sub>max</sub> )	7293 pg/mL*h	14.1		
	8	1000 µg Healthy	C <sub>max</sub> , AUC, mean PK profiles	3.8 nmol/L	3.8	17	10.5 nmol/L*h	10.5		Thorsson et al. (12)
		1000 µg Asthmatic		4.3 nmol/L	4.3	15	12.9 nmol/L*h	12.9		
	12	1000 µg Healthy	C <sub>max</sub> , AUC, mean PK profiles	NA	NA	NA	3.5 nmol/L*h	3.5	TBD	Thorsson et al. (16)

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