2.3 Study [redacted]09

A pharmacokinetic study to investigate the pharmacokinetics, safety and tolerability of a salmeterol/fluticasone propionate combinational product delivered via a novel multiple-dose dry powder inhaler (Pulmo Jet 50/500) compared to a marketed reference product (Seretide Diskus forte) administered with or without charcoal

Methods and objectives: Study [redacted]-09 was a randomised, open-label, single dose, 4-period crossover study in healthy adult subjects (PulmoJet SAL/FP high strength or Seretide Diskus forte with and without charcoal, Table 7). At each treatment day, subjects received four inhalations administered either by the PulmoJet SAL/FP high strength or the Seretide Diskus forte device. Treatments were separated by a washout-period of at least three days. Similar as in the initial pilot BA study [redacted]-01, the study was conducted in healthy adult male and female subjects. For further justifications of the study population see Module 2.5. Supratherapeutic single-doses (i.e. four sequential inhalations) were employed in order to ensure that observed C_{max} values would exceed the lower limit of quantification for both SAL and FP by at least 20-fold as recommended by the EMA guideline on the investigation of BE [6].

Table 7: Study [redacted]-09 - treatments

Treatment	Product	Metered dose SAL/FP [µg]	Posology	Total dose SAL/FP [µg]
Test	PulmoJet SAL/FP high	50/500	4 single inh.	200/2000
Test C	PulmoJet SAL/FP high	50/500 (+C)	4 single inh.	200/2000
Reference	Seretide Diskus forte	50/500	4 single inh.	200/2000
Reference C	Seretide Diskus forte	50/500 (+C)	4 single inh.	200/2000

C = charcoal, DD = delivered dose, FP = fluticasone propionate, inh. = inhalation, SAL = salmeterol.

Serial blood samples for PK assessments were taken pre-dose and up to 16 hours post dose for SAL, and up to 48 hours post-dose for FP. The primary objective was to investigate and compare the relative systemic bioavailability of SAL and FP after single dose administration, with and without charcoal, delivered by four actuations of the PulmoJet SAL/FP high strength test device and the Seretide Diskus forte reference device. The secondary objective was to investigate the bioavailability of SAL and FP after single dose administration delivered by four actuations of the PulmoJet SAL/FP high strength test device and the Seretide Diskus forte reference device taken together with and without activated charcoal comparing test with versus test without charcoal (TC versus T), and reference with versus reference without charcoal (RC versus R). Activated charcoal, which prevents the gastrointestinal absorption of the oropharyngeally deposited and subsequently swallowed fraction of the dose, was used to investigate the pulmonary bioavailability of the inhaled drug [7-9]. Specifically, 5.0 g of activated charcoal suspended in 50 mL water were administered 2 min before and 2 min after

administration of the test or reference product, followed by additional 10 g administrations (suspended in 100 mL of water) at 1, 2 and 3 hours post dose. Hence, the total dose of activated charcoal administered within about 3 hours around dosing was 40 g.

Study sites and EU authority inspections of study sites for study [redacted]-09 are listed in Table 8.

Table 8: Study [redacted]-09 - study sites

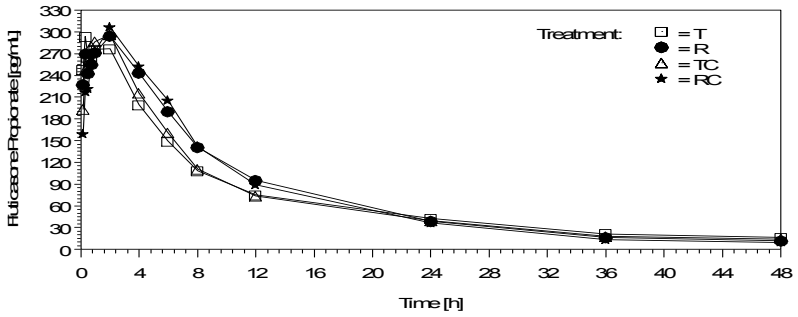
	Name	Address	EU Authority Inspection	
			Year	Authority
Clinical Study Site	[redacted]	[redacted]	[redacted]	[redacted]
Bioanalytical Study Site	[redacted]	[redacted]	[redacted]	[redacted]
PK and Statistical Analysis	[redacted]	[redacted]	[redacted]	[redacted]
Sponsor of the study	[redacted]	[redacted]	-	

Results: A total of 40 healthy adult Caucasian subjects were enrolled and randomly assigned to one of the four treatment sequences. Subjects (17 women and 23 men) were between 19 and 50 years of age and presented with a BMI between 20.6 and 28.9 kg/m^2.

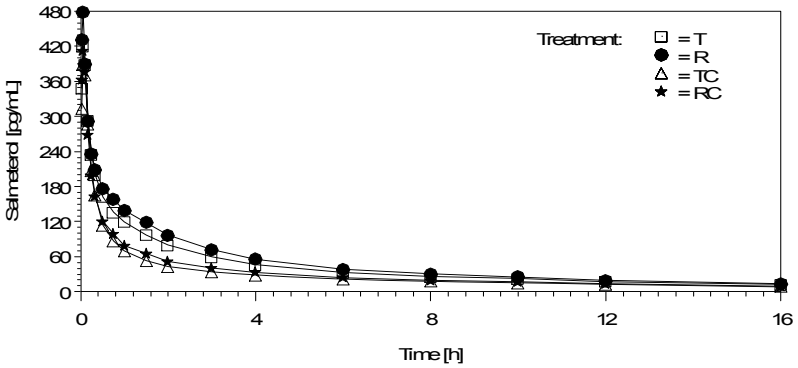
Mean concentration-time profiles of SAL and FP were similar after administration of the test treatment compared to the reference treatment under both treatment conditions, i.e. when administered either alone or together with charcoal (Figure 2).

Figure 2: Study [redacted]-09 - concentration-time profiles of salmeterol and fluticasone propionate

Fluticasone propionate



Salmeterol



R = reference (Seretide Disksu forte), RC = reference with charcoal (Seretide Diskus forte with charcoal), T = test (PulmoJet SAL/FP high), TC = test with charcoal (PulmoJet SAL/FP high with charcoal).
Data source: Module 5. 3.1.2, CSR [redacted] 09, Figure 11.4-1 and 11.4-4.

A summary of PK characteristics for SAL and FP for the test and reference products is provided in A-Table 4 and A-Table 5. A summary of comparative FP and SAL PK characteristics for the test and reference product administered alone or together with activated charcoal is provided in Table 9. For both FP and SAL the ratios and 90% CI for $AUC_{0\text{-tlast}}$, C_{max} and $AUC_{0\text{-}\infty}$ were within the standard BE acceptance range of 80% to 125%, for both treatment conditions with or without charcoal.

The effect of charcoal block on individual treatments revealed that for FP, charcoal did not influence extent of exposure for both test and reference. For SAL the extent of exposure was substantially reduced by concomitant charcoal administration for both the test and the reference product, indicating appreciable oral bioavailability of the swallowed fraction of SAL, while this was not the case for the FP component.

Table 9: **Study [redacted]-09 - Comparison between PulmoJet SAL/FP high strength and Seretide Diskus forte (analysis of variance) for PK parameters of fluticasone propionate and salmeterol**

Pharmacokinetic parameter	ANOVA-CV [%]	Test/ Reference	Point estimate [%]	90% CI [%]
Fluticasone proprionate				
$AUC_{0\text{-}tlast}$ [h pg/mL]	20.34	T/R	91.42	84.84 - 98.50#
		TC/RC	92.66	85.99 - 99.84#
		T/TC	100.67	93.43 - 108.47#
		R/RC	102.03	94.69 - 109.94#
C_{max} [pg/mL]	20.58	T/R	107.95	100.09 - 116.42#
		TC/RC	103.48	95.95 - 111.60#
		T/TC	103.32	95.80 - 111.43#
		R/RC	99.04	91.84 - 106.81#
$AUC_{0\text{-}\infty}$ [h·pg/mL]	20.45	T/R	95.28	88.39 - 102.70#
		TC/RC	97.08	90.06 - 104.64#
		T/TC	102.29	94.90 - 110.27#
		R/RC	104.23	96.69 - 112.35#
Salmeterol				
$AUC_{0\text{-}tlast}$ [h·pg/mL]	17.93	T/R	86.86	81.32 - 92.78#
		TC/RC	90.99	85.18 - 97.19#
		T/TC	148.03	138.58 - 158.12
		R/RC	155.06	145.17 - 165.63
C_{max} [pg/mL]	26.68	T/R	89.67	81.36 - 98.82#
		TC/RC	96.48	87.54 - 106.33#
		T/TC	107.44	97.48 - 118.41#
		R/RC	115.60	104.89 - 127.41
$AUC_{0\text{-}\infty}$ [h·pg/mL]	19.78	T/R	87.81	81.65 - 94.42#
		TC/RC	92.87	86.36 - 99.86#
		T/TC	144.82	134.67 - 155.73
		R/RC	153.17	142.43 - 164.71

# within the bioequivalence range of 80% to 125%.
ANOVA = anaylsis of variance, $AUC_{0\text{-}tlast}$ = area under the concentration time curve from zero to the last time point, $AUC_{0\text{-}\infty}$ = area under the plasma concentration-time data pairs extrapolated to infinity, CI = confidence interval, Cmax = maximum serum concentration, CV = coefficient of variance, PK = pharmacokinetic, R: Seretide Diskus forte (reference), RC: Seretide Diskus forte (reference) together with activated charcoal, T: Pulmo Jet high (test), TC: Pulmo Jet high (test) together with activated charcoal.
Data source: Module 5. 3.1.2, CSR [redacted]09, Table 11.4-7 and 11.4-8.

Conclusions: PulmoJet SAL/FP high and Seretide Diskus forte were shown to be bioequivalent with respect to $AUC_{0\text{-}t}$, C_{max}, and $AUC_{0\text{-}\infty}$ for both FP and SAL and for both treatment conditions with or without activated charcoal.

For SAL, the extent of exposure was substantially reduced by co-administration of activated charcoal, while this was not the case for FP. These outcomes were expected and in line with

published evidence on the known oral bioavailability of SAL and the negligible oral bioavailability of FP, thereby confirming the validity of the study conduct and the employed charcoal block methodology of the study.

For safety results see Module 2.7.4.

2.4 Study [redacted] 06

A multicenter, randomised, open-label, intra-subject/patient crossover study for acquiring inspiratory profiles with PulmoJet, Diskus and Turbuhaler dry powder inhaler devices in healthy adult subjects, children with asthma and adult patients with moderate to severe asthma and adult patients with moderate to very severe chronic obstructive pulmonary disease.

Methods and objectives: Study [redacted] 06 was a multi-centre, randomised, open-label, intra-subject crossover study for acquiring inspiratory profiles with the PulmoJet, the Diskus and the Turbuhaler in four different populations (healthy adults, children with asthma, adults with moderate to severe persistent asthma,[1] and adults with moderate to very severe COPD[2]). Inhalation flow rates as a function of time were assessed by measuring the subject-generated pressure drop within the mouthpiece, using a small drain tube, versus ambient pressure. The relationship between pressure drop and flow rate was assessed by a calibration curve for each DPI, determined with a flow/volume simulator. With each DPI each subject performed three inhalation maneuvers. The sequence of device use was randomised for each individual subject. The primary objective was to determine the peak inspiratory flow rates (PIF) generated through the respective devices and to show that patients representative of the anticipated target populations are able to attain a sufficient flow rate to release the trigger mechanism of PulmoJet. Secondary parameters included total inhaled volume, absolute and % inhaled volume to reach PIF, absolute and % inhaled volume after achievement of PIF, time to reach PIF, total inhalation time, mean inspiratory flow rate, time over which an inspiratory flow rate more than 80% of PIF was achieved, flow increase rate at 20, 40, 60, and 80% of PIF.

Study sites and EU authority inspections of study sites for study [redacted]-06 are listed in Table 10.

[1] Moderate asthma was defined as pre-bronchodilator FEV_1 between 60 and 80% predicted and FEV_1 reversibility ≥12% and ≥200 mL; severe asthma as pre-bronchodilator FEV_1 ≤60 %predicted and FEV_1 reversibility ≥12% and ≥200 mL)

[2] Moderate COPD was defined as post-bronchodilator FEV_1 between 50 and 80% predicted and FEV_1/FVC <70%; severe COPD as post-bronchodilator FEV_1 between 30 and 50% predicted and FEV_1/FVC <70%.