Synopsis

Title of the study:

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 (PulmoJet® 50/500) compared to a marketed reference product (Seretide Diskus® forte) administered with or without charcoal

Principal Investigator(s) and study center(s):

[redacted]

Coordinating investigator(s): not applicable

Publication (reference): Not applicable

Studied period: 11-Apr-2011 (first subject enrolled) to 01-Jun-2011 (last subject completed)

Clinical phase: phase I

Objectives:

Primary

- To investigate and compare the relative systemic bioavailability of a salmeterol/fluticasone propionate combinational product after single dose administration delivered by four actuations of the PulmoJet® 50/500 test device (test, T) and the Seretide Diskus® forte reference device (reference, R) administered with and without charcoal by comparing the test product to the corresponding reference product (T vs. R, TC vs. RC).

Secondary

- To investigate the bioavailability of salmeterol/fluticasone after single dose administration delivered by four actuations of the PulmoJet® 50/500 test device and the Seretide Diskus® forte reference device taken together with and without activated charcoal comparing TC versus T, RC versus R in order to quantify the charcoal effect.
- To assess and compare the local and systemic safety and tolerability of the test and reference treatments.

Methodology:

The study design is a randomized, open-label, single dose, 4-period crossover design with four treatment arms (T: test, R: reference, TC: test + charcoal, RC: reference + charcoal). Healthy subjects were randomized to one of the four treatment sequences. The subjects received all treatments (test and reference treatment at different occasions with and without

charcoal).

Number of subjects (planned and analyzed):

- Planned: 40; Included: 40; Drop-outs: 0
- Analyzed: 40 (safety), 40 (Pharmacokinetics)

Criteria for inclusion:

Healthy male and female subjects of any ethnic origin between 18 and 50 years of age (inclusive) with a body weight of ≥50 kg and a body mass index between 20 and 29 kg/m^2 (inclusive)

Test products, dose and mode of administration, batch number:

The salmeterol/fluticasone propionate combination was administered alone (T) or in combination with activated charcoal (TC).

PulmoJet® 50/500, salmeterol/fluticasone propionate combination dry powder inhaler

Metered dose per inhalation:	40 µg of salmeterol and 400 µg of fluticasone propionate
Dose:	single dose of 4 inhalations 1600 µg of fluticasone propionate 160 µg of salmeterol
Mode of administration:	oral inhalation
Batch no.:	[redacted]

Activated charcoal (Kohle-Compretten®)

Dose:	5 g (20 tablets) or 10 g (40 tablets)
Mode of administration:	oral
Batch nos.:	[redacted]

Reference products, dose and mode of administration, batch number:

The Seretide Diskus® forte was administered alone (R) or in combination with activated charcoal (RC).

Seretide Diskus® forte, 50 µg/500 µg/dose inhalation powder

Metered dose per inhalation:	50 µg of salmeterol and 500 µg of fluticasone propionate
Dose:	single dose of 4 inhalations 2000 µg of fluticasone propionate 200 µg of salmeterol
Mode of administration:	oral inhalation
Batch no.:	[redacted]

Activated charcoal (Kohle-Compretten®)

Dose: 5 g (20 tablets) or 10 g (40 tablets)
Mode of administration: oral
Batch nos.: [redacted]

Duration of treatment:

Single dose administration (4 inhalations) on Day 1 of each period separated by a washout phase of at least 3 days

Criteria for evaluation:

Pharmacokinetics

Confirmatory investigation of relative bioavailability (T vs. R, TC vs. RC)

Primary variables:

- AUC_{0-t} of fluticasone propionate and salmeterol

Secondary variables:

- C_{max}, $AUC_{0-\infty}$, AUC_{ext}, t_{max}, and $t_{1/2}$ of fluticasone propionate and salmeterol

Secondary Quantification of charcoal effect on bioavailability (TC vs. T, RC vs. R)

- AUC_{0-t}, C_{max}, $AUC_{0-\infty}$, AUC_{ext}, t_{max}, and $t_{1/2}$ of fluticasone propionate and salmeterol

Safety and tolerability

Adverse events, vital signs, safety laboratory, electrocardiogram, physical examination, local tolerability (inhalation related clinical signs and symptoms of paradoxical bronchospasm) and overall tolerability.

Statistical methods:

Pharmacokinetics

All measured variables and derived pharmacokinetic parameters were listed individually and, if appropriate, summarized by descriptive statistics.

The pharmacokinetic parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were logarithmically transformed and analyzed with analysis of variance (ANOVA) models with the factors treatment, sequence, period and subject within sequence. The parametric point estimates for the ratio test/reference and 90% confidence intervals were calculated using the least square means from the ANOVA of log-transformed data with subsequent exponential transformation.

Primary analysis

The test treatments T and TC were considered bioequivalent to the respective reference treatments R and RC, if the 90% confidence intervals for the AUC_{0-t} ratios lie within a range of 80% to 125%.

Secondary analysis

C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ were analyzed similarly to AUC_{0-t}.

Secondary quantification of charcoal effect on bioavailability

The effect of charcoal was determined by calculating the 90% confidence intervals for the AUC_{0-t}, C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$ ratios for the comparisons T/TC, R/RC. For fluticasone propionate, no difference of bioavailability between treatments with and without activated charcoal was expected due to low oral bioavailability (<1%) in contrast to salmeterol.

One ANOVA model was used for each of the two analytes salmeterol/fluticasone propionate and for each pharmacokinetic parameter. All least square means and corresponding confidence intervals were depicted from these estimations.

Safety

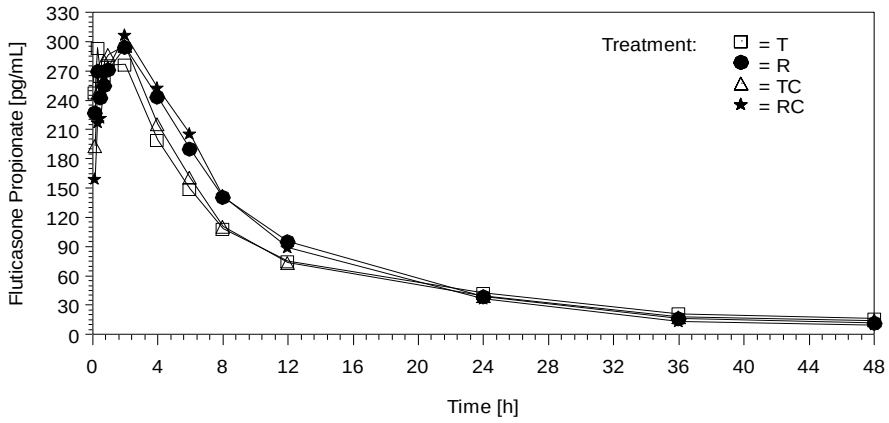
All safety and tolerability parameters were listed by subject and treatment and were analyzed by appropriate descriptive statistics.

During statistical evaluation of adverse events, a MedDRA statistic according to ICH, i.e. with assignment of adverse events to the categories “related” and “not related” were prepared. The causalities “possible”, “probable / likely” and “certain” were considered to be related to IMP treatment.

SUMMARY - CONCLUSIONS

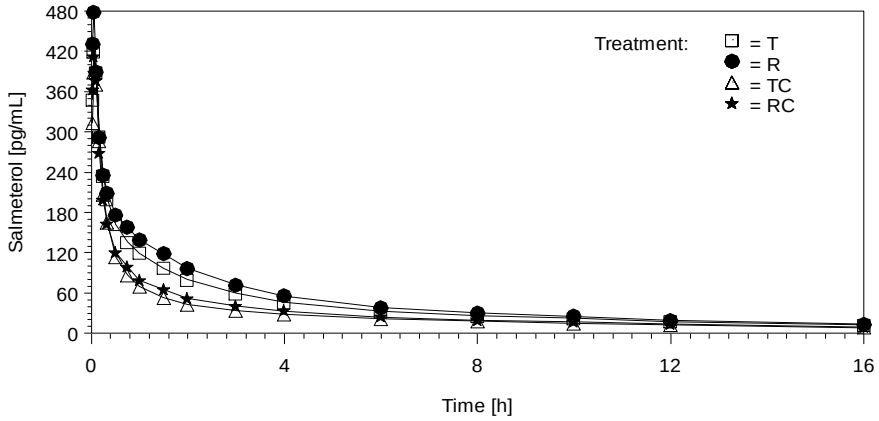
Pharmacokinetic results:

For either treatment (test, reference), mean concentration-time profiles of fluticasone proprionate were similar with or without activated charcoal. Mean concentration-time profiles were modestly lower under test treatment than under reference treatment (mainly within 2 to 12 h a.a.) with or without activated charcoal.



Source: Figure 14.2.1.1

Mean concentration-time profiles of salmeterol were similar after administration of the test treatment compared to the reference treatment when administered alone or together with charcoal. Lower profiles were observed for both treatments after administration of the respective treatment with charcoal.



Source: Figure 14.2.2.1

T: 4 inhalations of PulmoJet® 50/500, metered dose of 40/400 µg salmeterol/fluticasone propionate (test),
R: 4 inhalations of Seretide Diskus® forte, 50/500 µg salmeterol/fluticasone propionate (reference),
TC:4 inhalations of PulmoJet® 50/500, metered dose of 40/400 µg salmeterol/fluticasone propionate (test) together with activated charcoal (Kohle-Compretten®),
RC: 4 inhalations of Seretide Diskus® forte, 50/500 µg salmeterol/fluticasone propionate (reference) together with activated charcoal (Kohle-Compretten®)

The point estimates for all treatment ratios (i.e. T/R, TC/RC, T/TC, R/RC) and the respective 90% confidence intervals for AUC_{0-t}, C_{max}, and $AUC_{0-\infty}$ of fluticasone propionate were altogether entirely within the bioequivalence acceptance range of 80.00% to 125.00%.

The point estimates for the treatment ratios T/R and TC/RC and the respective 90% confidence intervals for AUC_{0-t}, C_{max}, and $AUC_{0-\infty}$ of salmeterol were altogether entirely within the bioequivalence acceptance range of 80.00% to 125.00%.

The point estimates for the treatment ratios T/TC for AUC_{0-t}, C_{max}, and $AUC_{0-\infty}$ of salmeterol were 148.03%, 107.44%, and 144.82%. For $C_{max,}$ the respective 90% confidence interval was entirely within the bioequivalence acceptance range of 80.00% to 125.00%

The point estimates for the treatment ratios R/RC for $AUC_{0-t,}$ C_{max}, and $AUC_{0-\infty}$ of salmeterol were 155.06%, 115.06%, and 153.17%. For C_{max}, the respective 90% confidence interval exceeded the upper acceptance limit of the bioequivalence range of 125.00%.

Pharmacokinetic Parameter fluticasone propionate	**ANOVA-CV [%]**	**Test/ Reference**	**Point estimate [%]**	**90% Confidence interval [%]**
AUC_{0-t} [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
$AUC_{0-\infty}$ [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
Pharmacokinetic Parameter salmeterol	**ANOVA-CV [%]**	**Test/ Reference**	**Point estimate [%]**	**90% Confidence interval [%]**
AUC_{0-t} [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
$AUC_{0-\infty}$ [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

T: 4 inhalations of PulmoJet® 50/500, metered dose of 40/400 µg salmeterol/fluticasone propionate (test),
R: 4 inhalations of Seretide Diskus® forte, 50/500 µg salmeterol/fluticasone propionate (reference),
TC:4 inhalations of PulmoJet® 50/500, metered dose of 40/400 µg salmeterol/fluticasone propionate (test) together with activated charcoal (Kohle-Compretten®),
RC: 4 inhalations of Seretide Diskus® forte, 50/500 µg salmeterol/fluticasone propionate (reference) together with activated charcoal (Kohle-Compretten®)

Safety results:

No death and no other serious adverse events occurred. None of the subjects discontinued the study due to an adverse event.

The frequency of treatment-emergent adverse events was low after administration of the test and reference treatment with 4 events reported by 4 of the 40 subjects (10.0%) after administration of the test product and 6 events reported by 5 of the 40 subjects (12.5%) after administration of the reference product. Under both treatments, 4 possibly drug-related treatment-emergent adverse events were reported by 4 subjects: 3 events of headache and one event of cough after the test product and 4 events of headache after the reference product.

More treatment-emergent adverse events were reported after administration of the test and reference product together with activated charcoal: After the test treatment, 10 events were reported by 5 subjects (12.5%) and after the reference treatment 9 events were reported by 6 subjects (15.0%). After administration of the test product together with activated charcoal 2 events of headache and 1 event each of dizziness, epistaxis, constipation, diarrhea, fatigue and hyperhidrosis were assessed as possibly related. After administration of the reference product together with activated charcoal 4 events of headache and 2 events of cough were assessed as possibly related. A similar proportion of subjects reported possibly related adverse events under the reference treatment (5 subjects, 12.5%) and under the test treatment (4 subjects, 10.0%).

The 3 events of cough occurred within 5 min after inhalation of the respective product and were considered to be inhalation-related local adverse events: one event occurred 1 min after end of inhalation of the reference treatment (when administered with activated charcoal) and two events occurred immediately after end of inhalation of the test and reference treatment (when the reference treatment was administered with activated charcoal), respectively.

Six subjects received paracetamol for the treatment of headache.

All events were resolved at the end of the study.

No clinically significant findings and no medically relevant changes were observed in regard to safety laboratory, vital signs and electrocardiogram evaluation.

The overall tolerability was assessed as good in all subjects.

Conclusions:

Pharmacokinetics

- Bioequivalence of the test and reference product could be demonstrated with 90% confidence intervals for the ratios (T/R) of AUC_{0-t}, C_{max}, and $AUC_{0-\infty}$ of fluticasone propionate and salmeterol within the bioequivalence acceptance range of 80.00% to 125.00% when the test and reference product were administered without activated charcoal.
- Bioequivalence could also be demonstrated when the test and reference product was administered with activated charcoal with 90% confidence intervals for the ratios (TC/RC) of AUC_{0-t}, C_{max}, and $AUC_{0-\infty}$ of fluticasone propionate and salmeterol within the bioequivalence acceptance range of 80.00% to 125.00%.
- The extent of fluticasone propionate exposure was unaltered for the test and reference product by co-administration of charcoal, i.e. 90% confidence intervals for the ratios (T/TC, R/RC) of AUC_{0-t}, C_{max} and $AUC_{0-\infty}$ were altogether entirely within the bioequivalence acceptance range of 80.00% to 125.00%.
- The total extent of exposure to salmeterol (i.e. AUC_{0-t}, and $AUC_{0-\infty}$) was about 48% and 55% higher (when AUC_{0-t} is considered) after administration of the test and reference products alone than after co-administration with activated charcoal. In contrast to the parameters of total exposure, the maximum exposure to salmeterol (i.e. C_{max}) was unaltered by charcoal co-administration when the test product is considered, and was only modestly elevated (i.e. about 15% on average) in case of the reference product.

Safety

- Inhalation of supratherapeutic single doses of fluticasone propionate (PulmoJet® 1600 µg and Seretide Diskus® forte 2000 µg) and salmeterol (PulmoJet® 160 µg and Seretide Diskus® forte 200 µg) via the PulmoJet® 50/500 dry powder inhaler and the marketed Seretide Diskus® forte dry powder inhaler was well tolerated by healthy male and female subjects in this study.
- The use of the PulmoJet® Inhaler was not associated with differences in the frequency or severity of adverse events as compared to the marketed Diskus® inhaler. No adverse events occurred that resulted from the use of the PulmoJet® Inhaler and the marketed Diskus® Inhaler with regard to technical aspects.
- The safety results observed in this study were in line with the current knowledge on the safety pharmacological profile of fluticasone propionate and salmeterol.

Date of report: 24-Oct-2011