1. TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY REPORT

Clinical Study Report Code: M/40468/00/R

Name of the investigational medicinal products: Seretide Accuhaler®
Charcodote®

Indication studied: Not applicable
Phase of the study: I

A PHASE I, RANDOMISED, OPEN LABEL, 4 WAY COMPLETE CROSSOVER, SINGLE DOSE PHARMACOKINETIC CLINICAL TRIAL FOR AN INHALED FIXED DOSE COMBINATION (LABA + ICS)

(Protocol No. M/40468/00; EudraCT No. 2011-000389-37)

Statistical Report No.: M/40468/00 Final Version 15 November 2011
Pharmacokinetics Report No.: B.40468.02 Final Version 29 May 2012
Date of initiation of the study: 11 May 2011
Date of completion of the study: 28 June 2011
Date of completion of the Report: 18 February 2013 (Final Version 2.0)

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The study was performed in accordance with Good Clinical Practices (GCP) including the archiving of essential documents

2. SYNOPSIS

Name of Sponsor / Company: Almirall, S.A. **Name of Finished Products:** Seretide Accuhaler®, Charcodote® **Name of Active Ingredients:** Salmeterol xinafoate and fluticasone propionate, activated charcoal	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

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Publication (reference):
None

Studied period (years): Date study initiated (first screening): 11 May 2011 Date study finalized (last subject last visit): 28 June 2011	**Phase of development:** I

Objectives:

- To assess the pharmacokinetics of single doses of salmeterol and fluticasone propionate of two different commercial batches of Seretide Accuhaler® 50/500 µg in healthy volunteers
- To assess the safety and tolerability of the study treatments.

Methodology:
This was a pilot, phase I, randomized, open label, 4 way complete crossover, single dose clinical trial to assess the pharmacokinetics of an inhaled fixed dose combination (LABA+ICS) of two different batches of Seretide Accuhaler® 50/500 µg administered with and without gastrointestinal absorption blockade by charcoal to healthy volunteers.
The study consisted of 4 periods of 1 treatment day separated by a washout period of at least 7 days.
At each treatment period, subjects received one of the following treatments: Seretide Accuhaler® 50/500 µg Batch 1 QD, Seretide Accuhaler® 50/500 µg Batch 2 QD, Seretide Accuhaler® 50/500 µg Batch 1 QD with Charcodote® and Seretide Accuhaler® 50/500 µg Batch 2 QD with Charcodote®.
Depending on the treatment sequence (A, B, C or D) the subject was assigned, subjects received the following:

Sequences	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
A (n=4)	SFP Batch 1 with charcoal	SFP Batch 1 without charcoal	SFP Batch 2 with charcoal	SFP Batch 2 without charcoal
B (n=4)	SFP Batch 2 with charcoal	SFP Batch 1 with charcoal	SFP Batch 2 without charcoal	SFP Batch 1 without charcoal
C (n=4)	SFP Batch 2 without charcoal	SFP Batch 2 with charcoal	SFP Batch 1 without charcoal	SFP Batch 1 with charcoal
D (n=4)	SFP Batch 1 without charcoal	SFP Batch 2 without charcoal	SFP Batch 1 with charcoal	SFP Batch 2 with charcoal

SFP: salmeterol fluticasone propionate (Seretide Accuhaler® 50/500 µg)

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After a screening evaluation within a period of 14 days, eligible subjects fulfilling inclusion/exclusion criteria were assigned to one of the 4 treatment sequences according to a William's design for crossover trials and using a balanced 1:1:1:1 randomization ratio.
Randomized subjects received the 4 different treatments in the EPCU and were subject to a schedule of blood collection for pharmacokinetic purposes, and safety and tolerability assessments. The duration of each treatment period was 24 hours (with a washout period of at least 7 days between treatments).
At the beginning of each period, subjects were assigned a Seretide Accuhaler® device. Subjects were instructed to take the IMP, at the clinic and under supervision, as 1 puff from the inhaler provided approximately at 09:00 ±1 hour in 4 different periods (there was a new device for each period). In 2 of the 4 periods, study medication was taken during a protocol of charcoal administration.
Training for optimum inhalation following Seretide Accuhaler® Patient Information Leaflet was performed at the Screening Visit and at the beginning of each visit (before dosing). Tools for training were provided per subject: a separate empty Accuhaler® device and an In-Check DIAL device. Standard fasting conditions and daily meals were applied at each treatment period.
The occurrence of adverse events during the washout periods and/or use of any concomitant medication were collected at each study visit.

Number of subjects (planned and analyzed):

Planned for randomization:	16 (4 per sequence)
Screened:	38
Randomized:	16 (4 per sequence)
Completed study:	16
Evaluated for PK:	16 (PK population)
Evaluated for safety:	16 (Safety population)

Diagnosis and main criteria for inclusion:

- Healthy male and female subjects, aged between 18 and 55 years.
- No clinically important abnormal physical findings at screening.
- No disease or condition with lung inflammatory processes.
- No gastrointestinal, hepatic or renal condition that could affect the systemic absorption, metabolism or elimination of the products under investigation.
- No recent medical history that would result at the time of randomization in any possible residual lung function limitation or upper airways/lung inflammatory process (e.g. cold/flu symptoms, lung infection, thoracic surgery).
- No clinically relevant abnormalities in the results of screening laboratory evaluation and screening ECG.
- Systolic blood pressure between 90 and 140 mmHg, diastolic blood pressure between 50 and 90 mmHg, heart rate between 45 and 90 bpm.
- Body Mass Index between 18.5 and 30 kg/m^2.
- Able to inhale appropriately through Accuhaler® device assessed through In-Check DIAL.
- Able to communicate well with the investigator and to comply with the requirements of the entire trial.
- Ability to understand and provision of a written informed consent document prior to any study related procedures are performed.
- No history of serious adverse reactions or hypersensitivity to any drug or contraindication to drugs pharmacologically related to the IMP.
- No intake of any IMP during the 30 days period prior to the first treatment period or simultaneous participation in another biomedical research study.
- Subjects that are non-smokers or ex-smokers (completely stopped smoking for at least 6 months) of less than 5 cigarettes a day.

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Test product, dose and mode of administration, batch number, expiry date:

Name IMP-1: Seretide Accuhaler® Batch 1
Administration route: Oral inhalation
Dosage form: Inhalation powder administered via Accuhaler®
Dose and regimen: 50 µg salmeterol and 500 µg fluticasone propionate, 1 puff as single dose; Batch number: R509100; Expiry date: April 2012

Name IMP-2: Seretide Accuhaler® Batch 2
Administration route: Oral inhalation
Dosage form: Inhalation powder administered via Accuhaler®
Dose and regimen: 50 µg salmeterol and 500 µg fluticasone propionate, 1 puff as single dose; Batch number: R508587; Expiry date: May 2012

Name IMP-3: Charcodote® (activated charcoal)
Administration route: Oral administration
Dosage form: Oral suspension
Dose and regimen: 200 mg/mL as per charcoal administration protocol; Batch number: 10K09; Expiry date: November 2012

Duration of treatment:

In total 4 days of treatment (1 per treatment period x 4 treatment periods) per subject.
The actual total duration of the study for each subject was approximately 6 to 7 weeks (including screening and follow-up telephone contact).

Reference therapy, dose and mode of administration, batch number, expiry date:

Not applicable

Criteria for evaluation:

Pharmacokinetics:

For each subject who participated in the study, the following pharmacokinetic parameters for salmeterol and fluticasone propionate were determined in plasma for each treatment batch and each administration condition (with and without charcoal): area under the concentration–time curve from zero to time t, where t is the time of the last concentration measured (AUC(0-t)), area under the concentration–time curve from zero to infinity (AUC), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration t_{max}, smallest (terminal) elimination rate constant (λ_z), elimination half-life ($t_{½}$), total body clearance from plasma after extravascular administration (CL/f), apparent volume of distribution during the terminal phase (Vz/f), and mean residence time (MRT).
λz and its derived pharmacokinetic parameters $t_{½}$, AUC, V_z/f, CL/f and MRT were estimated if the terminal disposition phase could be observed.
Pharmacokinetic parameters for salmeterol and fluticasone propionate were analyzed to estimate the relative bioavailability for the AUC and C_{max} between treatments and variance for each treatment.

Safety and Tolerability:

Adverse events (AEs), serious adverse events (SAEs), blood pressure (BP), 12-lead ECG (HR, PR, RR, QRS, QT, QTcB and QTcF intervals, and abnormal findings in the ECG tracing), clinical laboratory tests (standard hematology, blood chemistry, urinalysis and serum pregnancy test [female only]) and physical examination.

Other variables:

Number (%) of withdrawals and reasons for withdrawal, and prior and concomitant medication.

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Statistical methods:

The analysis of all pharmacokinetic parameters was performed on the PK analysis population. All analyses of safety outcomes and other variables were performed on the Safety population.

Pharmacokinetic parameters, safety and tolerability data (AEs, SAEs, blood pressure, laboratory parameters and ECG), subject's inhalation performance (as per In-Check DIAL), number and reasons for withdrawals, and concomitant medications were analyzed by means of the appropriate descriptive statistics across treatment groups.

Additionally, AUC(0-t), AUC and C_{max} were analyzed after log-transformation by means of analysis of covariance (ANCOVA) models for crossover designs. Estimates of treatment effects comparing the AUC(0-t), AUC and C_{max} of all different treatment comparisons was based on the ratio of the least square means and was presented on the untransformed scale with the associated 90% CI.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Below are the mean (±SD, CV%) pharmacokinetic parameters of salmeterol and fluticasone propionate following single inhalation of 50/500 µg (LABA/ICS) through the Seretide Accuhaler® device from commercial Batch 1 and Batch 2 with and without Charcodote®.

Compound	Parameters (units)	Seretide Accuhaler® Batch 1	Seretide Accuhaler® Batch 1 with Charcodote®	Seretide Accuhaler® Batch 2	Seretide Accuhaler® Batch 2 with Charcodote®
Salmeterol	C_{max} (pg/ml)	157 (±50.3, 32.0 %)	165 (±29.4, 17.8%)	128 (±54.6, 42.6%)	100 (±32.4, 32.3%)
	t_{max} (h)	0.083 (1) (0.083 - 0.12)	0.083 (1) (0.083 - 0.12)	0.083 (1) (0.083 - 0.15)	0.083 (1) (0.083 - 0.083)
	$t_{1/2}$ (h)	11.5 (±1.96, 17.0%)	10.8 (±1.93, 17.9%)	12.9 (±4.52, 35.2%)	9.77 (±2.53, 25.9%)
	λ_z (1/h)	0.0619 (±0.0103, 16.7%)	0.0660 (±0.0109, 16.5%)	0.0602 (±0.0212, 35.2%)	0.0757 (±0.0203, 26.9%)
	AUC(0-t) (pg.h/ml)	196 (±68.5, 35.0%)	183 (±42.0, 23.0%)	162 (±53.1, 32.7%)	114 (±35.6, 31.4%)
	AUC (pg.h/ml)	254 (±65.4, 25.8%)	218 (±55.8, 25.6%)	201 (±65.9, 32.8%)	135 (±42.4 31.4%)
	MRT (h)	12.3 (±2.17, 17.6%)	11.2 (±2.41, 21.5%)	13.2 (±4.48, 33.9%)	10.0 (±2.69, 26.8%)
	CL/f (l/h)	207 (±46.1, 22.2%)	244 (±60.7, 24.9%)	274 (±91.2, 33.3%)	414 (±163, 39.3%)
	V_z/f (l)	3416 (±859, 25.2%)	3722 (±827, 22.2%)	4848 (±1752, 36.1%)	5567 (±1818, 32.7%)

(1) Median value (minimum - maximum value).

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Compound	Parameter (Units)	Seretide Accuhaler® Batch 1	Seretide Accuhaler® Batch 1 with Charcodote®	Seretide Accuhaler® Batch 2	Seretide Accuhaler® Batch 2 with Charcodote®
Fluticasone propionate	C_{max} (pg/ml)	130	126	99.6	82.4
		(±39.1,	(±31.0,	(±30.4,	(±24.9,
		30.2%)	24.6%)	30.6%)	30.3%)
	t_{max} (h)	1.5(1)	1.5(1)	1.5(1)	1.5(1)
		(0.5 - 2)	(0.5 - 4)	(0.5 - 2)	(0.5 - 2)
	$t_{1/2}$ (h)	7.25	7.64	7.36	7.18
		(±1.20,	(±1.08,	(±0.909,	(±1.01,
		16.6%)	14.2%)	12.4%)	14.0%)
	λ_z (1/h)	0.0989	0.0925	0.0956	0.0981
		(±0.0217,	(±0.0131,	(±0.0120,	(±0.0122,
		21.9%)	14.2%)	12.6%)	12.5%)
	AUC(0-t) (pg.h/ml)	1209	1236	885	700
		(±370,	(±242,	(±244,	(±202,
		30.6%)	19.6%)	27.5%)	28.8%)
	AUC (pg.h/ml)	1359	1400	988	776
		(±423,	(±274,	(±273,	(±229,
		31.1%)	19.6%)	27.7%)	29.6%)
	MRT (h)	10.2	10.8	10.1	9.70
		(±1.46,	(±1.58,	(±1.55,	(±1.25,
		14.4%)	14.6%)	15.3%)	12.8%)
	CL/f (l/h)	667	374	541	710
		(±1242,	(±93.1,	(±145,	(±252,
		186%)	24.9%)	26.7%)	35.4%)
	V_z/f (l)	5545	4086	5734	7336
		(±6984,	(±1019,	(±1782,	(±2815,
		126%)	24.9%)	31.1%)	38.4%)

(1) Median value (minimum - maximum value).

One subject, corresponding to Batch 1 without Charcodote® treatment, showed a very low concentration-time profile for both components in comparison to the other subjects of this group of treatment. The AUC(0-t) value calculated for this subject was 4.9% for salmeterol and 6.4% for fluticasone propionate, of the geometric mean AUC(0-t) in the same group of treatment. Data for this subject were not excluded from the above two tables of results.

Safety and Tolerability Results:

- Single inhaled morning doses of SFP Batches 1 and 2 with and without charcoal showed a good safety and tolerability profile in healthy male and female subjects.

- Overall, 8 (50%) subjects reported 12 TEAEs. Most of these TEAEs were considered by the investigator to be of mild (9) intensity, while 3 TEAEs were moderate. The number and percentage of subjects with at least one TEAE was similar across the treatment groups, with 2 (13%), 3 (19%), 4 (25%) and 2 (13%) after SFP Batch 1 with charcoal, SFP Batch 1 without charcoal, SFP Batch 2 with charcoal and SFP Batch 2 without charcoal, respectively. The number of TEAEs per treatment group was also similar with 2, 4, 4 and 2 TEAEs, respectively.

- The most frequently reported TEAE was headache with 6 events (occurring in 3 patients: 2 events

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after each SFP Batch 1 and 2 with charcoal and 1 event after each SFP Batch 1 and 2 without charcoal). The next most frequent reported TEAE was back pain, with 2 events (occurring in 2 patients: 1 event after each SFP Batch 1 and 2 without charcoal). Six TEAEs (5 headaches and 1 hiccup) were considered by the Investigator to be related to the IMP and the remaining 6 TEAEs to be not related.

- There were no SAEs or deaths and no AEs leading to subject withdrawal from the study.
- There was no clinically significant effect on any safety laboratory parameter and no laboratory results constituted a TEAE.
- No clinically relevant changes in systolic and diastolic blood pressure were observed in any treatment group.
- No clinical relevant changes were observed in heart rate or any other of the 12-lead ECG parameters in any treatment group.

CONCLUSIONS:

- Following inhalation of Seretide Accuhaler® 50/500 µg Batch 1, there were no differences in the rate (C_{max}) and extent (AUC) of absorption of salmeterol or fluticasone propionate in treatments with and without charcoal.
- However, after inhalation of Seretide Accuhaler® 50/500 µg Batch 2, lower C_{max} and AUC values for both salmeterol and fluticasone propionate components were observed when inhalation was carried out in the presence of charcoal. The differences in salmeterol concentration were observed in the whole concentration-time profile including the first 30-60 minutes which reflect primarily pulmonary absorption.
- There were no relevant trends between treatments in the estimated salmeterol mean half-life values and a low to moderate degree of variability was observed across treatments.
- Batch comparison within treatments (Batch 1 with charcoal vs Batch 2 with charcoal and Batch 1 without charcoal vs Batch 2 without charcoal) always resulted in higher salmeterol and fluticasone propionate exposure for Batch 1 than for Batch 2. These results may reflect some degree of variability in systemic exposure when different batches of Seretide Accuhaler® 50/500 µg are compared.
- Overall, and as expected for marketed IMPs, single inhaled morning doses of Seretide Accuhaler® Batch 1 and Batch 2, each administered with and without charcoal, were safe and well tolerated in healthy male and female subjects.

DATE OF REPORT:
18 February 2013 (Final Version 2.0)