1. TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY REPORT

Clinical Study Report Code: M/40468/01/R

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

Indication studied: Not applicable
Phase of the study: I

A PHASE I, RANDOMIZED, OPEN LABEL, 6-WAY COMPLETE CROSSOVER, SINGLE DOSE, COMPARATOR CONTROLLED, PHARMACOKINETIC CLINICAL TRIAL FOR AN INHALED FIXED DOSE COMBINATION (LABA+ICS)

(Protocol No. M/40468/01; EudraCT No. 2011-006153-29)

Statistical Report No.: M/40468/01, 08 January 2013
Pharmacokinetics Report No.: B.40468.03, 20 June 2013
Date of initiation of the study: 20 March 2012
Date of completion of the study: 05 May 2012
Date of completion of the Report: 25 November 2013 (V. 4.0)

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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:** LAS40468 Genuair®, Seretide Accuhaler®, Charcodote® **Name of Active Ingredients:** Salmeterol xinafoate/ fluticasone propionate fixed-dose combination via Genuair® (LAS40468); Seretide Accuhaler® and activated charcoal	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of Study: A PHASE I, RANDOMIZED, OPEN LABEL, 6-WAY COMPLETE CROSSOVER, SINGLE DOSE, COMPARATOR CONTROLLED, PHARMACOKINETIC CLINICAL TRIAL FOR AN INHALED FIXED DOSE COMBINATION (LABA+ICS)

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Publication (reference):
None

Studied period (years):	**Phase of development:** I
Date study initiated (first screening): 20 March 2012 Date study finalized (last subject last visit): 05 May 2012	

Objectives:

Primary objective:

- To assess the pharmacokinetics of single doses of two different formulations of salmeterol xinafoate/fluticasone propionate fixed-dose combination (FDC) via Genuair® and Seretide® Accuhaler® 50/500 µg when administered with and without charcoal in healthy volunteers.

Secondary objectives:

- To assess the bioequivalence between two different test formulations of salmeterol/fluticasone propionate FDC via Genuair and the reference product Seretide Accuhaler 50/500 µg when administered with and without charcoal in healthy volunteers.
- To assess the safety and tolerability of the study treatments.

Methodology:
This was a phase I, randomized, open-label, 6-way complete crossover, single-dose clinical trial to assess the pharmacokinetics (PK) of two different test formulations of salmeterol/fluticasone propionate FDC via Genuair and Seretide Accuhaler 50/500 µg administered with and without charcoal to healthy volunteers.
The study consisted of 6 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:

1. LAS40468 50/500 µg: (Salmeterol/fluticasone propionate FDC via Genuair)
2. LAS40468 50/500 µg: (Salmeterol/fluticasone propionate FDC via Genuair) with charcoal
3. LAS40468 22/370 µg: (Salmeterol/fluticasone propionate FDC via Genuair)
4. LAS40468 22/370 µg: (Salmeterol/fluticasone propionate FDC via Genuair) with charcoal
5. Seretide Accuhaler 50/500 µg
6. Seretide Accuhaler 50/500 µg with charcoal

Subjects received the following treatments according to the sequence they had been allocated to:

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Sequences	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4	Treatment Period 5	Treatment Period 6
A (n = 3)	LAS40468 22/370 μg with charcoal	LAS40468 22/370 μg without charcoal	LAS40468 50/500 μg with charcoal	LAS40468 50/500 μg without charcoal	Seretide Accuhaler with charcoal	Seretide Accuhaler without charcoal
B (n = 3)	LAS40468 22/370 μg without charcoal	LAS40468 50/500 μg without charcoal	LAS40468 22/370 μg with charcoal	Seretide Accuhaler without charcoal	LAS40468 50/500 μg with charcoal	Seretide Accuhaler with charcoal
C (n = 3)	LAS40468 50/500 μg without charcoal	Seretide Accuhaler without charcoal	LAS40468 22/370 μg without charcoal	Seretide Accuhaler with charcoal	LAS40468 22/370 μg with charcoal	LAS40468 50/500 μg with charcoal
D (n = 3)	Seretide Accuhaler without charcoal	Seretide Accuhaler with charcoal	LAS40468 50/500 μg without charcoal	LAS40468 50/500 μg with charcoal	LAS40468 22/370 μg without charcoal	LAS40468 22/370 μg with charcoal
E (n = 3)	Seretide Accuhaler with charcoal	LAS40468 50/500 μg with charcoal	Seretide Accuhaler without charcoal	LAS40468 22/370 μg with charcoal	LAS40468 50/500 μg without charcoal	LAS40468 22/370 μg without charcoal
F (n = 3)	LAS40468 50/500 μg with charcoal	LAS40468 22/370 μg with charcoal	Seretide Accuhaler with charcoal	LAS40468 22/370 μg without charcoal	Seretide Accuhaler without charcoal	LAS40468 50/500 μg without charcoal

After a screening evaluation, within a period of 14 days, 18 eligible subjects fulfilling inclusion/exclusion criteria were assigned to one of the six treatment sequences according to a William's design for crossover trials and using a balanced 1:1:1:1:1:1 randomization ratio.

Once randomized, subjects received a single dose of each of the six different treatments in the EPCU separated by at least 7 days. Each inhalation (one inhalation per treatment period) was preceded and followed by pharmacokinetic sampling, as well as by some safety and tolerability assessments. In addition, when activated charcoal was part of the treatment, a specific charcoal administration protocol was followed before and after inhalation. The duration of each treatment period was 24 hours (washout period of at least 7 days between treatments).

At the beginning of each period subjects were provided with a new inhaler according to their randomized treatment: either a Genuair or a Seretide Accuhaler inhaler. Subjects were instructed to take the Investigational Medicinal Product (IMP) at the clinic and under supervision. One inhalation from the inhaler was administered at approximately 09:00 ±1 h in six different periods (there was a new inhaler for each period). In three of the six periods IMP was taken during a protocol of charcoal administration.

Tools for training were provided per subject: a separate Accuhaler and Genuair inhaler containing placebo, and an In-Check DIAL device. Standard fasting conditions and daily meals were applied at each treatment period.

The occurrence of adverse events (AEs) during the washout periods and/or use of any concomitant medication were collected at each study visit.

Number of subjects (planned and analysed):

Planned for randomization: 18 (3 per sequence)

Screened: 34

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Randomized:	18 (3 per sequence)
Completed study:	15
Evaluated for PK:	18 (PK population)
Evaluated for safety:	18 (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 electrocardiogram (ECG).
- Systolic blood pressure between 90 and 140 mmHg, diastolic blood pressure between 50 and 90 mmHg, heart rate (HR) between 45 and 90 bpm.
- Body Mass Index between 18.5 and 30 kg/m^2.
- Able to inhale appropriately through Genuair and Accuhaler inhalers as assessed through In-Check DIAL.
- Able to communicate well with the Investigator and to comply with the requirements of the entire trial.
- Provision of written informed consent to participate prior any trial procedure as shown by signature on the subject consent form.
- 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 were non-smokers or ex-smokers (completely stopped smoking for at least 6 months) of less than 5 pack/year.

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

Name IMP-1:	LAS40468
Administration route:	Oral inhalation
Dosage form:	Inhalation powder administered via Genuair
Dose and regimen:	22 µg salmeterol and 370 µg fluticasone propionate, 1 inhalation as a single dose; Batch number: K15-95-L82 (MCN148); Expiry date: November 2012
Name IMP-2:	LAS40468
Administration route:	Oral inhalation
Dosage form:	Inhalation powder administered via Genuair
Dose and regimen:	50 µg salmeterol and 500 µg fluticasone propionate, 1 inhalation as a single dose; Batch number: K15-94-L83 (MCN148); Expiry date: November 2012
Name IMP-3:	Seretide Accuhaler
Administration route:	Oral inhalation
Dosage form:	Inhalation powder administered via Accuhaler
Dose and regimen:	50 µg salmeterol and 500 µg fluticasone propionate, 1 inhalation as a single

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dose; Batch number: R551481-L85 (MCN148); Expiry date: November 2012

Name IMP-4: Charcodote® (activated charcoal)
Administration route: Oral administration
Dosage form: Oral suspension
Dose and regimen: 200 mg/mL (40 g/day) as per charcoal administration protocol; Batch number: 11L13; Expiry date: 31 December 2013

Duration of treatment:
In total 6 days of treatment (1 per treatment period x 6 treatment periods) per subject.
The total duration of the study for each subject was to be of approximately 9 weeks (including screening and follow-up telephone contact). There was a screening period of maximum 14 days followed by 6 periods of 1 treatment day separated by a minimum washout period of 7 days and a follow-up visit (phone contact) 7 (±2) days after last treatment day or after premature discontinuation visit.

Reference therapy, dose and mode of administration, batch number, expiry date:
IMP-3 was the reference product, which was a commercialized batch of the Seretide Accuhaler 50/500 µg (for details refer to "Test product, dose and mode of administration, batch number, expiry date").

Criteria for evaluation:

Pharmacokinetics:
For each subject who participated in the trial, the following pharmacokinetic parameters of 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).
λ_z and its derived pharmacokinetic parameters $t_{½}$, AUC, V_z/f, CL/f and MRT were estimated if the terminal disposition phase could be characterized well.

Safety and Tolerability:
The safety and tolerability outcomes of this study consisted of 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; during the treatment periods only HR and QTcF were collected for analysis), clinical laboratory tests (standard hematology, blood chemistry, and urine pregnancy test [female only]), glucose and potassium (bedside test), and physical examination. In addition, urinalysis (dipstick, sediment) was only performed at screening.

Other variables:
Other variables included peak inspiratory flow (PIF) (L/min) from In-Check DIAL, number (%) of withdrawals and reasons for withdrawal, and prior and concomitant medication.

Statistical methods:
The analysis of all PK 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, HR and QTcF), subject's inhalation performance (as per In-Check DIAL), number and

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reasons for withdrawals, prior and concomitant medications were analyzed by means of the appropriate descriptive statistics across treatment groups.
Additionally, the bioequivalence of each test formulation of salmeterol xinafoate/fluticasone propionate FDC via Genuair versus the reference product Seretide Accuhaler 50/500 µg in the two different conditions (with and without charcoal) was assessed. Furthermore the relative bioavailability between the two test formulations (LAS40468 22/370 µg and LAS40468 50/500 µg) and between the two conditions (with and without charcoal) were assessed.
The analysis of AUC(0-t), AUC and C_{max} was based on an analysis of variance (ANOVA) model on the log-transformed pharmacokinetic parameters. Since two different formulations were tested, a Bonferroni procedure was applied and consequently a 95% ($\alpha = 0.025$) confidence interval (CI) for the difference between each test formulation vs. reference on the log-transformed scale was obtained from the ANOVA model. This CI was then back-transformed to obtain the desired CI for the ratio on the original scale. Bioequivalence was concluded if the corresponding CIs were within 80.00% – 125.00%.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Below are the mean (±SD, CV%) pharmacokinetic parameters of salmeterol and fluticasone propionate following single inhalation of LABA/ICS through the Seretide Accuhaler (50/500 µg) and the Genuair device (50/500 µg or 22/370 µg) with and without charcoal treatment:

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Compound	**Para-meters (units)**	**Seretide Accuhaler 50/500 µg**		**LAS40468 50/500 µg (salmeterol/fluticasone propionate 50/500 µg via Genuair)**		**LAS40468 22/370 µg (salmeterol/fluticasone propionate 22/370 µg via Genuair)**	
		without charcoal	**with charcoal**	**without charcoal**	**with charcoal**	**without charcoal**	**with charcoal**
		N=16	**N=17**	**N=17**	**N=17**	**N=16**	**N=17**
Salmeterol (LAS31420)	**C_{max} (pg/ml)**	176 (±71.3 40.5%)	165 (±63.8 38.7%)	494 (±187 37.8%)	488 (±166 34.0%)	246 (±69.7 28.4%)	204 (±82.8 40.6%)
	t_{max} [(1)] (h)	0.067 (0.033 - 0.1)	0.067 (0.058 - 0.1)	0.067 (0.061 - 0.11)	0.073 (0.033 -0.1)	0.067 (0.056 -0.1)	0.0769 (0.041 -0.1)
	$t_{1/2}$ (h)	9.71 (±1.11 11.5%)	10.2 (±2.23 21.7%)	10.5 (±1.57 15.0%)	11.3 (±3.11 27.5%)	10.4 (±2.00 19.2%)	10.3 (±2.15 20.9%)
	λ_z (1/h)	0.0723 (±0.00835 11.5%)	0.0708 (±0.0156 22.1%)	0.0677 (±0.0107 15.9%)	0.0651 (±0.0162 24.9%)	0.0690 (±0.0145 21.0%)	0.0704 (±0.0155 22.0%)
	AUC(0-t) (pg.h/ml)	211 (±87.1 41.2%)	171 (±59.8 34.9%)	487 (±193 39.8%)	462 (±158 34.1%)	238 (±84.0 35.3%)	200 (±66.4 33.1%)
	AUC (pg.h/ml)	246 (±98.8 40.2%)	201 (±66.5 33.1%)	572 (±224 39.2%)	546 (±171 31.4%)	283 (±96.9 34.2%)	235 (±76.4 32.5%)
	MRT (h)	10.3 (±1.65 16.1%)	10.5 (±2.59 24.6%)	10.7 (±1.98 18.5%)	11.3 (±3.09 27.3%)	10.8 (±2.55 23.6%)	10.4 (±2.41 23.1%)
	CL/f (l/h)	235 (±89.5 38.2%)	279 (±98.6 35.4%)	104 (±48.1 46.4%)	102 (±40.9 40.0%)	90.0 (±42.6 47.3%)	107 (±47.7 44.6%)
	V_z/f (l)	3263 (±1212 37.1%)	4132 (±1677 40.6%)	1586 (±826 52.1%)	1746 (±1066 61.1%)	1307 (±488 37.3%)	1542 (±572 37.1%)

(1) Median value (min.-max. value).

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Compound	**Para-meters (units)**	**Seretide Accuhaler 50/500 µg**		**LAS40468 50/500 µg (salmeterol/fluticasone propionate 50/500 µg via Genuair)**		**LAS40468 22/370 µg (salmeterol/fluticasone propionate 22/370 µg via Genuair)**	
		without charcoal	**with charcoal**	**without charcoal**	**with charcoal**	**without charcoal**	**with charcoal**
		N=16	**N=17**	**N=17**	**N=17**	**N=16**	**N=17**
Fluticasone propionate (LAS186822)	**C_{max} (pg/ml)**	130 (±41.2 31.8%)	123 (±35.9 29.3%)	186 (±56.0 30.0%)	185 (±45.2 24.4%)	173 (±41.1 23.8%)	136 (±42.7 31.4%)
	t_{max} (1) (h)	0.75 (0.1 -2)	1 (0.25 -3)	0.75 (0.25 - 3)	1 (0.1 -3)	1 (0.5 -2)	1 (0.25 - 2)
	$t_{1/2}$ (h)	8.15 (±1.18 14.5%)	7.86 (±1.16 14.8%)	9.43 (±1.17 12.4%)	8.99 (±1.60 17.8%)	8.74 (±1.07 12.3%)	8.61 (±1.16 13.5%)
	λ_z (1/h)	0.0868 (±0.0131 15.1%)	0.0899 (±0.0122 13.6%)	0.0746 (±0.00912 12.2%)	0.0792 (±0.0126 15.9%)	0.0804 (±0.0100 12.4%)	0.0819 (±0.0110 13.4%)
	AUC(0-t) (pg.h/ml)	1053 (±320 30.4%)	1004 (±275 27.4%)	1511 (±424 28.1%)	1491 (±386 25.9%)	1329 (±355 26.7%)	1080 (±343 31.7%)
	AUC (pg.h/ml)	1202 (±370 30.8%)	1145 (±330 28.9%)	1796 (±531 29.5%)	1760 (±507 28.8%)	1545 (±412 26.7%)	1253 (±409 32.6%)
	MRT (h)	10.7 (±1.65 15.4%)	10.6 (±1.85 17.4%)	12.0 (±1.94 16.1%)	11.6 (±2.19 18.9%)	11.2 (±1.69 15.1%)	11.1 (±1.80 16.2%)
	CL/f (l/h)	454 (±139 30.6%)	476 (±151 31.7%)	305 (±102 33.3%)	311 (±109 34.9%)	258 (±79.9 30.9%)	330 (±116 35.2%)
	V_z/f (l)	5295 (±1627 30.7%)	5325 (±1602 30.1%)	4066 (±1118 27.5%)	3912 (±1084 27.7%)	3234 (±920 28.4%)	4050 (±1383 34.2%)

(1) Median value (min.-max. value).

- Following single inhalation of salmeterol/fluticasone propionate 50/500 µg via Seretide Accuhaler or via Genuair, with or without activated charcoal treatment, salmeterol t_{max} occurred at 4 min and fluticasone propionate t_{max} occurred between 0.75 h (45 min) and 1 h post dose.

- There were no relevant trends between treatments in the estimated mean half-life values of salmeterol, averaging 9.71 to 11.3 h, with a CV across the different treatments between 11.5% and 27.5%. Similarly, there were no relevant trends between treatments in the estimated mean half-life values of fluticasone propionate, averaging 7.86 to 9.43 h, with CV across the different treatments between 12.3% and 17.8%.

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- Coadminstration of charcoal had no relevant effect on the rate (C_{max}) and extent (AUC) of absorption of salmeterol or fluticasone propionate following inhalation of salmeterol/fluticasone propionate 50/500 µg via Seretide Accuhaler or via Genuair

- Following treatment with LAS40468 22/370 µg both C_{max} and AUC(0-t) for salmeterol or fluticasone propionate showed lower values (about 20%) when inhalation was carried out in presence of charcoal. In case of salmeterol, those differences were observed in the whole concentration-time profile (including the early kinetic time-points) with semi-logarithmic concentration-time curves from treatments with and without charcoal providing parallel slopes without any evidence of drug disposition phase masking due to the contribution of the oral absorption. In case of fluticasone propionate, given its negligible oral bioavailability (<1%) the differences observed were considered not related to the oral absorption of the drug.)

Bioequivalence Results:

- For most assessments of bioequivalence, the 95% confidence intervals of the mean salmeterol and fluticasone propionate AUC(0-t), AUC and C_{max} ratios fell outside the standard bioequivalence acceptance criteria range of 0.8 to 1.25 and for most comparisons, the ratio itself was also outside this range.

- When comparing LAS40468 22/370 µg versus Seretide Accuhaler 50/500 µg without charcoal, the ratio (and associated 95% confidence interval) for AUC(0-t) of salmeterol was inside the bioequivalence acceptance range: 1.093 [0.967 – 1.236]. Also within the bioequivalence range were fluticasone propionate AUC and AUC(0-t) (in the presence of charcoal): values 1.088 [0.949 – 1.247] and 1.068 [0.935 – 1.22] respectively.

Safety and Tolerability Results:

- Single inhaled morning doses of LAS40468 22/370 µg, LAS40468 50/500 µg and Seretide Accuhaler 50/500 µg, each administered with and without charcoal in a 6-way complete crossover design, showed a good safety and tolerability profile in the healthy male and female subjects.

- Overall, 9 (50%) subjects reported 33 TEAEs, most of which were considered by the Investigator to be of mild (23) intensity, while 10 TEAEs were considered to be moderate.

- The number and percentage of subjects with at least one TEAE was generally similar across the treatment groups.

- The most frequently reported TEAE was headache, with 12 events in 5 (27.8%) different subjects, followed by nausea, with 6 events in 3 (16.7%) different subjects and diarrhea, with 3 events in 3 (16.7%) different subjects. All other TEAEs occurred once or twice.

- A total of 24 TEAEs were considered by the Investigator to be related to the IMP, and the remaining 9 TEAEs to be not related.

- There were no SAEs or deaths, no severe AEs and no AEs leading to subject withdrawal from the

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study.

- There was no clinically significant effect on any safety laboratory parameter and no laboratory results constituted a TEAE. However, a slight increase in plasma glucose mean (at 30 min post-dose) was observed after LAS40468 50/500 µg (with and without charcoal).

- No clinically relevant changes in systolic and diastolic blood pressure were observed in any treatment group.

- No clinical relevant changes were observed in HR or QTcF in any treatment group or overall.

CONCLUSIONS:

- Pharmacokinetic data of this study show that oral absorption of salmeterol has no impact on the plasma concentration-profiles obtained following inhalation. LAS40468 administration with charcoal is not considered necessary for future studies.

- Bioequivalence analyses showed that:
    - LAS40468 22/370 ug and LAS40468 50/500 µg were not bioequivalent to Seretide 50/500 µg for both components.

- Overall, single doses of LAS40468 22/370 µg, LAS40468 50/500 µg and Seretide Accuhaler 50/500 µg, were safe and well tolerated in healthy male and female subjects.

DATE OF REPORT:
25 November 2013 (V. 4.0)