1. TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY REPORT

Clinical Study Report Code: M-40468-02

Name of the investigational medicinal products:
Seretide Accuhaler® and
Salmeterol (as xinafoate)/fluticasone propionate FDC via Genuair® (LAS40468)
Indication studied: Not applicable
Phase of the study: I

A PILOT, PHASE I, RANDOMIZED, OPEN LABEL, 4-WAY CROSSOVER, SINGLE DOSE CLINICAL TRIAL TO ASSESS THE PHARMACOKINETICS OF AN INHALED FIXED DOSE COMBINATION PRODUCT (LABA/ICS) DELIVERED BY TWO DIFFERENT INHALERS IN HEALTHY SUBJECTS.

(Protocol No. M-40468-02; EudraCT No. 2012-003377-26)

Statistical Report No.: M/40468/02/R 3 May 21013
Pharmacokinetics Report No.: 13 Dec 2013
Date of initiation of the study: 7 Jan 2013
Date of completion of the study: 11 Feb 2013
Date of completion of the Report: 28 May 2014

Company / Sponsor:
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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:** Salmeterol (as xinafoate)/fluticasone propionate fixed-dose combination via Genuair® (LAS40468) **Name of Active Ingredients:** Salmeterol and fluticasone propionate	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Title of Study: A PILOT, PHASE I, RANDOMIZED, OPEN LABEL, 4-WAY CROSSOVER, SINGLE DOSE CLINICAL TRIAL TO ASSESS THE PHARMACOKINETICS OF AN INHALED FIXED DOSE COMBINATION PRODUCT (LABA/ICS) DELIVERED BY TWO DIFFERENT INHALERS IN HEALTHY SUBJECTS		
Investigators: Principal Investigator: [redacted] PAREXEL International GmbH		
Study center: PAREXEL International GmbH Early Phase Clinical Unit (EPCU) - Berlin On the premises of the DRK Kliniken Berlin Westend, Haus 31 Spandauer Damm 130 14050 Berlin Germany		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 7 Jan 2013 Date study finalized (last subject last visit): 11 Feb 2013	**Phase of development:** I	

Objectives:

Primary objective:

- To compare the pharmacokinetics (PK) of single doses of three different formulations of salmeterol (as xinafoate)/fluticasone propionate fixed-dose combination (FDC) via Genuair® and of Seretide® Accuhaler® 50/500 µg.

Secondary objectives:

- To assess the safety and tolerability of the study treatments.

Methodology:

This was a phase I, randomized, open-label, 4-way complete crossover, single-dose clinical trial to assess the PK of three different test formulations of salmeterol/fluticasone propionate FDC via Genuair and of Seretide Accuhaler 50/500 µg administered to healthy volunteers.

The study consisted of four periods of 1 treatment day (follow-up of 36 hours) separated by a washout period of at least 3 days from the time of Investigational Medicinal Product (IMP) administration:

1. LAS40468 18/280 µg: (salmeterol/fluticasone propionate FDC via Genuair)
2. LAS40468 18/300 µg: (salmeterol/fluticasone propionate FDC via Genuair)
3. LAS40468 20/320 µg: (salmeterol/fluticasone propionate FDC via Genuair)
4. Seretide Accuhaler 50/500 µg

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

	Treatment Period 1	**Treatment Period 2**	**Treatment Period 3**	**Treatment Period 4**
Sequence A (n=4)	LAS40468 18/280 µg	LAS40468 18/300 µg	LAS40468 20/320 µg	Seretide Accuhaler 50/500 µg
Sequence B (n=4)	LAS40468 18/300 µg	Seretide Accuhaler 50/500 µg	LAS40468 18/280 µg	LAS40468 20/320 µg
Sequence C (n=4)	Seretide Accuhaler 50/500 µg	LAS40468 20/320 µg	LAS40468 18/300 µg	LAS40468 18/280 µg
Sequence D (n=4)	LAS40468 20/320 µg	LAS40468 18/280 µg	Seretide Accuhaler 50/500 µg	LAS40468 18/300 µg

LAS40468 = salmeterol/fluticasone propionate via Genuair

After a screening evaluation, within a period of 21 days, eligible subjects fulfilling inclusion/exclusion criteria were assigned to one of the four treatment sequences according to a William's design for crossover trials and using a balanced 1:1:1:1 randomization ratio.
Once randomized, subjects received the four different treatments in the EPCU separated by at least 3 days. Each inhalation (one inhalation per treatment period) was preceded and followed by PK sampling, as well as by some safety and tolerability assessments at the last treatment period. The duration of each treatment period was 36 hours with a washout period of at least 3 days between treatments.
At the beginning of each period subjects were provided with the inhaler according to their treatment: a Genuair or an Accuhaler inhaler. Subjects were instructed to take the IMP, at the clinic and under supervision, 1 inhalation from the inhaler provided approximately at 09:00 ±1 hour in four different periods.
Tools for training were provided to subjects: two inhalers (one Accuhaler and one Genuair) containing placebo, and an In-Check DIAL device. Subjects were trained with the relavant inhaler before dosing with the IMP. Standard fasting conditions and daily meals were applied at each treatment period.
The occurrence of adverse events (AEs) during the washout period 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:	31
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 pulmonary, 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, asthma or Chronic Obstructive Pulmonary Disease [COPD]).
- No clinically relevant abnormalities in the results of screening laboratory evaluation and screening electrocardiogram (ECG).
- Normal values at the screening pulmonary function test.
- Normal systolic and diastolic blood pressure and normal heart rate (HR).

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- Body Mass Index (BMI) 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.
- Subjects who understood and signed an Informed Consent document prior to any study-related procedures were 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 were non-smokers or ex-smokers (completely stopped smoking for at least 6 months) of less than 5 pack-years (number of cigarettes smoked per day × number of years smoked)/20.

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:	18 µg salmeterol (as xinafoate) and 280 µg fluticasone propionate, 1 inhalation as a single dose; Batch number: K15-116-L118; Expiry date: Mar 2013
Name IMP-2:	LAS40468
Administration route:	Oral inhalation
Dosage form:	Inhalation powder administered via Genuair
Dose and regimen:	18 µg salmeterol (as xinafoate) and 300 µg fluticasone propionate, 1 inhalation as a single dose; Batch number: K15-115-L117; Expiry date: Mar 2013
Name IMP-3:	LAS40468
Administration route:	Oral inhalation
Dosage form:	Inhalation powder administered via Genuair
Dose and regimen:	20 µg salmeterol (as xinafoate) and 320 µg fluticasone propionate, 1 inhalation as a single dose; Batch number: K15-117-L119; Expiry date: Mar 2013
Name IMP-4:	Seretide Accuhaler
Administration route:	Oral inhalation
Dosage form:	Inhalation powder administered via Accuhaler
Dose* and regimen:	50 µg salmeterol (as xinafoate) and 500 µg fluticasone propionate, 1 inhalation as a single dose; Batch number: 4486-L120; Expiry date: Mar 2013 for the IMP label but January 2014 according to Pharmaceutical Development documentation i.e. report FT1212 (see Appendix 16.1.1)

*Salmeterol dosage corresponding to salmeterol as free base.

Note:	When referring to the product name salmeterol in the text of this CSR, this includes salmeterol as xinafoate.

Duration of treatment:

In total four single dose treatments: (one per treatment period) per subject. The duration of each treatment period was of at least 36 hours.

The total duration of the trial for each subject was planned to be approximately between 3.5 to 8 weeks (including screening and follow-up telephone contact). There was a screening period of maximum 21 days followed by four periods of 1 single-dose treatment separated by a washout period of 3 to

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10 days and a follow-up 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:
The reference product was IMP-4, which was a commercialized batch of Seretide Accuhaler 50/500 µg (for details refer to the above section "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 PK parameters of salmeterol and fluticasone propionate were determined in plasma for each treatment batch: 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 ($t_{½}$).
The λz and its derived PK parameters $t_{½}$ and AUC were estimated if the terminal disposition phase was well characterized.

Safety and Tolerability:
The safety and tolerability outcomes of this study consisted of AEs, serious AEs (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, and urine pregnancy test [female only]).

Other variables:
Other variables included peak inspiratory flow (PIF) (L/min) from In-Check DIAL (at each corresponding setting) at Screening Visit and pre-dose, 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.
In this pilot study, the bioequivalence of each Test formulation of salmeterol/fluticasone propionate FDC via Genuair versus the Reference Seretide Accuhaler 50/500 µg was assessed as the primary analysis. The analysis of AUC(0-t) and C_{max} were based on an analysis of variance (ANOVA) model on the log-transformed PK parameters. For AUC(0-t) and C_{max}, the 90% confidence interval (CI) for the ratio between treatments were estimated using bioequivalence methodology.
Additionally safety and tolerability data (AEs, SAEs, blood pressure, laboratory parameters, ECGs), subject's inhalation performance (as per In-Check DIAL), number and reasons for withdrawals, prior and concomitant medications were analyzed by means of the appropriate descriptive statistics across treatment groups and/or overall.

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SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

The table below display the mean (standard deviation [±SD], %CV) PK parameters of salmeterol following single inhalation of salmeterol/fluticasone propionate FDC 50/500 µg via Seretide Accuhaler and 20/320 µg, 18/300 µg and 18/280 µg via Genuair

Compound	Parameters (units)		Seretide Accuhaler 50/500 µg (N=16)	Genuair 20/320 µg (N=16)	Genuair 18/300 µg (N=16)	Genuair 18/280 µg (N=16)
	C_{max}	Mean	104	168	171	153
	(pg/mL)	SD	54.6	58.4	45.0	50.7
		%CV	52.3	34.8	26.2	33.2
	t_{max}	Median	0.0745	0.0890	0.0945	0.0870
	(h)	Min	0.067	0.046	0.067	0.056
		Max	0.1	0.1	0.11	0.17
	$t_{1/2}$	Mean	12.3	13.8	13.6	13.5
	(h)	SD	1.67	1.83	1.99	2.19
Salmeterol		%CV	13.5	13.3	14.6	16.2
	λ_z	Mean	0.0572	0.0510	0.0517	0.0523
	(1/h)	SD	0.00787	0.0066	0.00580	0.00771
		%CV	13.8	12.9	11.2	14.7
	AUC(0-t)	Mean	176	211	214	208
	(pg.h/ml)	SD	50.7	44.0	42.0	44.6
		%CV	28.8	20.9	19.6	21.5
	AUC	Mean	195	240	240	235
	(pg.h/ml)	SD	57.5	55.4	47.0	54.4
		%CV	29.4	23.2	19.5	23.2

Source: Appendix 16.6, Table 11

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The table below display the mean (±SD, %CV) PK parameters of fluticasone propionate following single inhalation of salmeterol/fluticasone propionate FDC 50/500 µg via Seretide Accuhaler and 20/320 µg, 18/300 µg and 18/280 µg via Genuair

Compound	Parameters (units)		Seretide Accuhaler 50/500 µg (N=16)	Genuair		
				20/320 µg (N=16)	18/300 µg (N=16)	18/280 µg (N=16)
Fluticasone propionate	C_{max}	Mean	70.1	133	120	113
	(pg/ml)	SD	28.2	49.2	34.8	46.0
		%CV	40.2	37.1	29.0	40.7
	t_{max}	Median	1.5	1	1	1
	(h)	Min	0.5	0.25	0.5	0.5
		Max	3	3	3	4
	$t_{1/2}$	Mean	11.5	13.2	13.6	12.9
	(h)	SD	3.93	2.68	2.10	2.38
		%CV	34.2	20.4	15.4	18.5
	λ_z	Mean	0.0660	0.0545	0.0522	0.0558
	(1/h)	SD	0.0192	0.00981	0.00831	0.0112
		%CV	29.1	18.0	15.9	20.0
	AUC(0-t)	Mean	729	1095	1078	944
	(pg.h/ml)	SD	288	366	310	295
		%CV	39.5	33.5	28.7	31.2
	AUC	Mean	812	1235	1217	1061
	(pg.h/ml)	SD	321	442	362	336
		%CV	39.5	35.8	29.7	31.7

Source: Appendix 16.6, Table 12

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- Following inhalation of a fixed dose combination of salmeterol/fluticasone propionate via Seretide Accuhaler (50/500 µg) or via Genuair inhaler at three different dosages (18/280 µg, 18/300 µg or 20/320 µg) salmeterol t_{max} occurred in approximately 4 to 6 min and fluticasone propionate t_{max} occurred in approximately 1 to 1.5 h.

- Salmeterol exhibited a biphasic decline of the plasma concentrations, with an estimated elimination half-life of approximately 12-14 h. In contrast, fluticasone propionate exhibited a monoexponential decline with a similar half-life (12-14 h).

- Drug disposition profiles and elimination rate constants were consistent for salmeterol and fluticasone propionate across all treatments and independent of the device used for inhalation.

- Seretide treatments generally resulted in lower C_{max} values and lower AUC(0-t) values for both constituents than those of Genuair 18/280 µg, 18/300 µg or 20/320 µg.

- The bioequivalence comparison of the three Genuair FDC doses (test) versus Seretide treatment (reference) showed that in all cases the 90% CI were not contained within the acceptance interval for bioequivalence of 0.8-1.25.

- In general, the variability observed in the plasma levels of salmeterol and fluticasone propionate were higher following inhalation through Sereride Accuhaler than those obtained through the three tested fixed dose combinations of the Genuair inhaler.

Safety and Tolerability Results:

- Single inhaled morning doses of salmeterol/fluticasone propionate via Genuair 18/280 µg, 18/300 µg, 20/320 µg and Seretide Accuhaler 50/500 µg, administered in a 4-way complete crossover design, showed a good safety and tolerability profile in the healthy male and female subjects.

- Overall, 3 (18.8%) subjects reported 3 TEAEs during this study.

- All 3 TEAEs were headaches, which were considered by the Investigator to be related to the IMP; with 1 event considered of mild intensity (Genuair 18/280 µg) and 2 events considered of moderate intensity (Genuair 20/320 µg).

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

- There was no clinically significant effect on any safety laboratory parameter and none of the laboratory results were considered by the Investigator to be AEs.

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

- No clinically relevant changes were observed in ECG parameters (HR, QTcB or QTcF).

- No clinically relevant changes were observed in physical examination findings.

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CONCLUSIONS:

- Drug disposition profiles and elimination rate constants were consistent for salmeterol and fluticasone propionate across all treatments and independent of the device used for inhalation.
- Bioequivalence analyses of this pilot study showed that:
  - Salmeterol/fluticasone propionate via Genuair 18/280 µg, 18/300 µg and 20/320 µg were not bioequivalent to Seretide 50/500 µg.
- Overall, single inhaled morning doses of salmeterol/fluticasone propionate via Genuair 18/280 µg, 18/300 µg and 20/320 µg, and Seretide Accuhaler 50/500 µg were safe and well tolerated in healthy male and female subjects.

DATE OF REPORT:
28 May 2014 (Final 1.0)