FINAL CLINICAL STUDY REPORT

Title: A multicenter, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover, single dose study, comparing the efficacy and safety of the Fluticasone/Salmeterol combination administered with Elpen*haler*® (Rolenium®) versus the innovative one (Seretide Diskus®) in patients with asthma.

Name of test drug/ investigational product:	Rolenium®
Indication studied:	Asthma
Study design:	Multicenter, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover, single dose study.
Sponsor:	Elpen Pharmaceutical Co. Inc.
Study Code:	2007-FLUSAL-EL-01
EudraCT Number:	2008-000193-21
Development phase of study:	III
Study initiation date:	First patient enrolled : 12th November 2008
Study completion date:	Last patient completed : 13th February 2009
Name and affiliation of sponsor's responsible medical officer:	Dr Katerina Athanassiou, Pharmacist PhD Clinical Trials Director, Elpen Pharmaceutical Co. Inc. 95, Marathonos Av. 190 09 Pikermi, Athens, Greece Tel: +30 210 6039326 Fax: +30 210 6039300 Website: www.elpen.gr
Date of the report:	26/10/2009

STATEMENT

The trial was conducted in accordance with the ethical principles of the 18th World Medical Association Declaration (Helsinki, 1964) and all subsequent amendments and guidelines on Good Clinical Practice. Additionally, the clinical trial protocol complies with the laws and legislations of the country in which the study was conducted, all relevant guidelines, as well as those dealing with protection of personal data.

1 TITLE

A multicenter, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover, single dose study, comparing the efficacy and safety of the Fluticasone/Salmeterol combination administered with Elpen*haler*® (Rolenium®) versus the innovative one (Seretide Diskus®) in patients with asthma.

2 SYNOPSIS

Name of Sponsor/Company: Elpen Pharmaceutical Co. Inc.	**SYNOPSIS**	
Name of Finished Product: Rolenium®		
Name of Active Ingredient: Fluticasone/Salmeterol		

Study Title:

A multicenter, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover, single dose study, comparing the efficacy and safety of the Fluticasone/Salmeterol combination administered with Elpen*haler*® (Rolenium®) versus the innovative one (Seretide Diskus®) in patients with asthma.

Principal Investigators:	**Co-investigators:**
• Dr. Zoltán Kuberka • Dr. Katalin Gömöri • Dr. Éva Radeczky • Dr. Erzsébet Juhász	• Dr. Ilona Góhér • Dr. Judit Appel • Dr. Magdolna Póczi • Dr. Gabriella Temesi • Dr. Szabolcs Sótér • Dr. Peter Timor

Study centres:

- 2nd Pulmonary Outpatient Clinic of "Gyorgyir XI", Medical Care Public Benefit Organization, Budapest, Hungary
- Hospital "Dr. Kenessey Albert", Balassagyarmat, Hungary
- Men for Care Ltd. Szazhalom Medical Care Center, Szazhalombatta, Hungary
- National "Koranyi"Institute of Tuberculosis and Pulmonology department XIV, Budapest, Hungary

Publication (reference):

No scientific publication was annotated based on the whole or part of the study results till completion of the present report (September 2009).

Studied period: 3 months	**Phase of development:**
First patient enrolled: 12/11/2008 Last patient completed: 3/02/2009	Phase III (therapeutic confirmatory)

Objectives:

Primary

– To establish the therapeutic equivalence between the Fluticasone/Salmeterol combination administered with Elpen*haler*® (Rolenium®) and the innovative one (Seretide Diskus®) in terms of bronchodilator effect in lung function.

Secondary

– To establish the superiority of Fluticasone/Salmeterol combination administered with Elpen*haler*® (Rolenium®) over placebo in terms of bronchodilator effect in lung function.

– To compare the safety profile of the two Fluticasone/Salmeterol formulations in patients with asthma.

Methodology:

This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover, single dose, non-inferiority study.

Number of patients:

Number of patients planned to be recruited: 42

Number of patients enrolled: 42

Number of patients analysed: ITT population: 38

PP population: 33

Safety population: 42

Diagnosis and main criteria for inclusion:

Inclusion Criteria

Age 18-65, diagnosis of asthma of ≥ 6 months, FEV_1 ≥ 50% and ≤80% predicted, reversibility of at least 12%, stable asthma for at least 4 weeks, inhaled steroids (ICS) at a stable dose within the previous 30 days, PIF 30 - 90 lt/min and informed consent.

Exclusion Criteria

History of other pulmonary disease, asthma exacerbation or respiratory infection within the previous 4 weeks, hospitalization for acute asthmatic symptoms requiring parenteral steroids or oral steroid dose increase within the previous 30 days, heavy smokers, change of asthma medication within the previous 4 weeks, seasonal asthma alone, history of severe heart disease, pregnancy or lactation, use of a β-blocker, of a NSAID or an antiallergic/antihistaminic medication within 2 weeks prior to screening visit.

Test product:

Rolenium® Elpenhaler ® (Fluticasone/Salmeterol) DPI (Elpen Pharmaceutical Co. Inc.)

Dose: 250/50 μg

Mode of administration: Inhalation

Batch number: 80308

Duration of treatment:

The present was a single dose study.

Reference therapy 1:

Seretide® Diskus ® (Fluticasone/Salmeterol) DPI (GlaxoSmithKline)

Dose: 250/50 µg

Mode of administration: Inhalation

Batch number: R:320990

Reference therapy 2:

Placebo

Dose: Not applicable

Mode of administration: Inhalation

Criteria for evaluation:

Efficacy:

Primary Efficacy:

– 12-hour average FEV_1 [area under the FEV_1 versus time curve divided by 12 (FEV_1 AUC_{0-12}/12)].

Secondary Efficacy:

– The FEV_1 values over time for the 12-hour observation period.
– Peak FEV_1 value.
– Time to peak FEV_1 value.

Safety:

– Incidence of Adverse Events
– Changes in laboratory values (hematology and biochemistry)
– Changes in the 12-lead ECG
– Changes in vital signs
– Incidence of paradoxical bronchospasm

Statistical methods:

Primary Efficacy:

Therapeutic equivalence of Elpen*haler*® (Rolenium®) to the innovative (Seretide Diskus®) is declared if the 2-sided 95% Confidence Interval of ($\ln X_t$ - $\ln X_r$) is a subset of [-0.223, 0.223], where the X_t and X_r stand for the 12-hour average FEV_1 of test and reference product respectively (FEV_1 AUC_{0-12}/12) in the natural logarithmic scale.

Secondary Efficacy:

Mixed models approach was used to assess the superiority of Test therapy over Placebo in terms of FEV_1 AUC_{0-12}/12, the time course of FEV_1 and Peak FEV_1. Time

to Peak FEV_1 was assessed by non parametric analysis of variance.

Safety Analysis

No inferential statistical analysis was performed for the safety. Adverse Events were coded according to MedDRA 11.0 dictionary and are presented in summary tables. Summary statistics was performed of the evaluation of laboratory measurement.

Summary Conclusions:

Primary Efficacy:

ITT Population

The difference of FEV_1 $AUC_{0-12}/12$ in the logarithmic scale between Elpen*haler*® (Rolenium®) and the Seretide Diskus® was found to be 0.01316 whereas the 95%Confidence Interval of the difference was [-0.019480 0.04580]. Since this is a subset of [-0.223 0.223] the non inferiority of Elpen*haler*® (Rolenium®) over the Seretide Diskus® can be concluded. When values were antiloged the Test over Reference product ratio of FEV_1 $AUC_{0-12}/12$ was 101.3% 95% Confidence Interval: [98.1% 104.7%]$\subseteq$ [80% 125%].

PP Population

Test over Reference product ratio of FEV_1 $AUC_{0-12}/12$ was 101.3% 95%Confidence Interval: [98.2% 104.6%]$\subseteq$ [80% 125%].

Secondary Efficacy:

Superiority of Test over Placebo

The FEV_1 $AUC_{0-12}/12$ of the Test treatment group was found to be significantly greater compared to the Placebo group (Table S 1), p= 0.026.

Table S 1: FEV_1 $AUC_{0-12}/12$ Test over Placebo treatment (antilogs)

	Mean	95% Confidence Interval
Test	2.2069	[2.1029 2.3161]
Placebo	2.0970	[1.9981 2.2008]

The time course between Test and Reference drugs

The time course of FEV_1 during the study for the Elpenhaler® (Rolenium®) over the Seretide® Discus® is graphically represented below (**Figure S1**). Treatment outcome was not significantly different for the two groups over the period of 720 minutes, p=0.2258

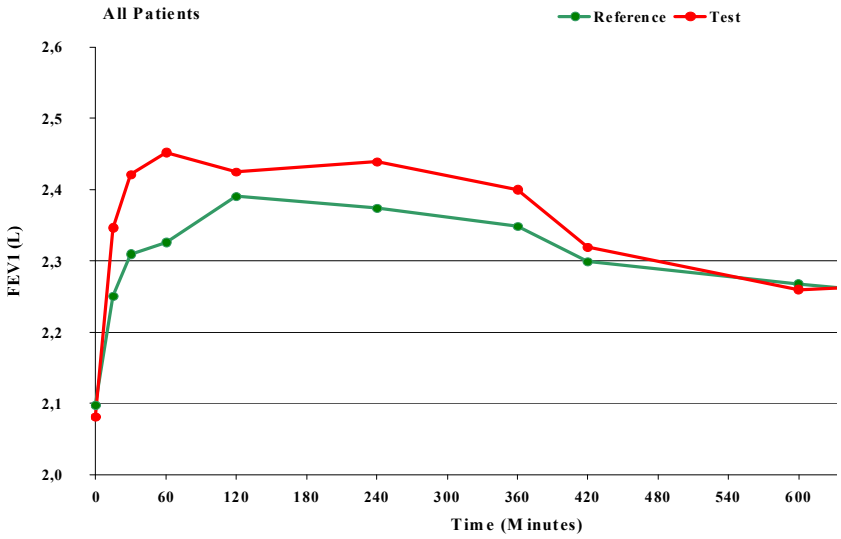

Figure S 1. Time Course of Test and Reference drugs

Table S 2: Least Square Estimates FEV_1 treatment difference between groups (Test and Reference) over the study period.

Time	Geometric Mean FEV_1 (L)	95% Confidence Interval	p
0 min	0.9833	[0.9416 1.0268]	0.4427
15 min	1.0326	[0.9889 1.0783]	0.1451
30 min	1.0320	[0.9883 1.0777]	0.1525
60 min	1.0404	[0.9963 1.0864]	0.0729
120 min	1.0124	[0.9696 1.0572]	0.5734
240 min	1.0247	[0.9813 1.0701]	0.2667
360 min	1.0240	[0.9807 1.0693]	0.2801
420 min	1.0061	[0.9635 1.0507]	0.7802
600 min	0.9846	[0.9429 1.0282]	0.4804
720 min	1.0051	[0.9625 1.0495]	0.8183

Peak FEV_1

The Peak of FEV_1 did not differ between the Test and Reference treatment groups (p=0.483), see **Table S 3**.

Table S 3 : Summary statistics of Peak FEV_1 (L)

	Mean	95% Confidence Interval
Reference	2.3736	[2.2687 2.4831]
Test	2.4051	[2.2993 2.5161]

Time to Peak FEV_1

The median time to peak FEV_1 did not differ significantly between Test and Reference group, p=0.3184, see following table **(Table S 4)**.

Table S 4: Summary statistics of Time to Peak FEV_1

	Minimum	25th	Median	75th	Maximum
Placebo	15	15	60	240	720
Reference	15	120	120	480	720
Test	15	60	120	360	720

Safety Results:

In total, 4 adverse events occurred in the current study; 2 of them in placebo group (headache and dyspnoea) and 2 of them in the Test treatment group (facial numbness and headache). All adverse events were non- serious, mild in severity and patients fully recovered after suitable treatment; see following table (**Table S 5**).

Table S 5: Adverse Events occurred during the course of the study and after randomization.

Patient Number	Treat-ment Group	AE Term	Date of Onset / Date Ended	Severity	Relation-ship to treatment	Action taken	Outcome
0304	Placebo	Headache	24/11/08 / 24/11/08	Mild	Not Related	Treatment for AE	Recovered
0308	Placebo	Dyspnoea	13/12/08 / 13/12/08	Mild	Not Related	Treatment for AE	Recovered
0403	Test	Facial Numbness	12/01/09 / 12/01/09	Mild	Not Related	None	Recovered
0406	Test	Headache	13/01/09 / 13/01/09	Mild	Not Related	Treatment for AE	Recovered

No clinically significant changes in the measurements taken in the blood analysis and biochemistry and no clinically significant ECG abnormalities were observed according to the investigators.

CONCLUSION:

The primary objective of the study was to establish the therapeutic equivalence of the Fluticasone/Salmeterol combination (250/50 µg) when administered with Elpen*haler*® (Rolenium®) against the innovative Diskus DPI (Seretide Diskus®). Their equivalence was shown via assessment of their bronchodilator effect, with FEV_1 $AUC_{0-12}/12$ as

primary variable and peak FEV_1 and time to peak FEV_1 as secondary variables. Therapeutic equivalence between Rolenium® and Seretide Diskus® (non-inferiority test) and superiority of Rolenium® over placebo was supported by the data and analyses presented in this report. In accordance with the efficacy analyses, analyses of safety variables after receiving each treatment also concluded on no additional safety issues arising when using Elpen*haler*® instead of Diskus® for administering Fluticasone/Salmeterol combination. Thus Rolenium® and Seretide Diskus® present a similar safety profile.

The results of the present study confirm that the administration of Fluticasone/Salmeterol combination via Elpen*haler*® (Rolenium®) and Seretide Diskus® is equivalent, exhibiting comparable bronchodilator activity in patients with asthma.

Date of the report: 26 / October / 2009

Version: 1.0