2. SYNOPSIS

Title of study:	A multicenter, randomized, double-blind, double-dummy, 2-way crossover, single dose study, comparing the efficacy and safety of the Fluticasone/Salmeterol (500/50 µg) combination administered with Elpen*haler*® (Rolenium®) versus the innovative one (Seretide Diskus®) in patients with asthma.
Clinical phase:	III
Investigators	01 - PI Bouckova M.D. 02 - PI Skacel M.D. 03 - PI Zindr M.D. 04 - PI Veverka M.D. 05 – PI Baly M.D. 06 - PI Fousek M.D. 07 - PI Joura M.D. 08 - PI Dindos M.D.
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Study period	27/Mar/2008 – 23/Jun/2008

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 their bronchodilator effect in lung function. Secondary – 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, 2-way crossover, single dose, non-inferiority study.
Number of subjects (planned and analysed):	The study was planned to enroll 24 evaluable patients in order to demonstrate the non-inferiority of the new formulation versus the reference formulation, at two sided 5% level of significance. To adjust for about 10% withdrawals and major protocol violations, the total size of the sample will be comprised of 28 patients. A total of 30 patients were screened and 28 were enrolled in the study. All 28 patients completed the study and included in the ITT population and safety population. 26 patients included in the PP population
Diagnosis and main criteria for inclusion:	Inclusion Age 18-65, diagnosis of asthma of ≥ 6 months, $FEV_1 \geq 50\%$ 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 l/min and informed consent. Exclusion 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® (Fluticasone/Salmeterol) DPI (Elpen Pharmaceutical Co. Inc.)
Dose:	500/50 µg
Method of administration:	Inhalation
Duration of treatment:	This was a single dose study comprising 2 treatment visits. The maximum length of the treatment period (including wash-out periods) was estimated to be 17 days.
Reference therapy 1:	Seretide® (Fluticasone/Salmeterol) DPI (GlaxoSmithKline)
Dose:	500/50 µg
Method of administration:	Inhalation
Criteria for evaluation:	
Efficacy:	Primary – The primary variable was the 12-hour average FEV_1 [area under the FEV_1 versus time curve divided by 12 (FEV_1 AUC_{0-12}/12)].

<table>
<tr><td></td><td>Secondary
– The FEV_1 values over time for the 12-hour observation period.
– Peak FEV_1 value.
– Time to peak FEV_1 value.</td></tr>
<tr><td>Safety:</td><td>– Adverse Events
– Changes in laboratory values (hematology and biochemistry)
– Changes in the 12-lead ECG.
– Changes in vital signs.
– Paradoxical bronchospasm</td></tr>
<tr><td>Statistical methods:</td><td>Primary efficacy variable:
Non-inferiority of Elpenhaler® (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.
Secondary efficacy variable:
Generalized linear model appropriate for cross-over designs allowing random and fixed effects was emplyed for the secondary efficacy end points. All tests were two sided and the statistical significance level was set at 5%</td></tr>
<tr><td>Summary</td><td></td></tr>
<tr><td>Primary efficacy end point</td><td>In the ITT population the mean FEV_1 AUC_{0-12}/12h was found 2.739 ± 0.706 for the reference product and 2.675 ± 0.643 for the test product, respectively. The difference of the mean FEV_1 AUC_{0-12}/12h between the test and the reference formulation was -0.064 ± 0.238. These values are summarized in the Table below
<table>
<tr><td></td><td>FEV_1 AUC_{0-12}/12h Reference</td><td>FEV_1 AUC_{0-12}/12h Test</td><td>Difference (Test – Reference)</td></tr>
<tr><td>N</td><td>28</td><td>28</td><td></td></tr>
<tr><td>Min</td><td>2.009</td><td>1.929</td><td>-0.080</td></tr>
<tr><td>Max</td><td>4.691</td><td>4.460</td><td>-0.231</td></tr>
<tr><td>Mean</td><td>2.739</td><td>2.675</td><td>-0.064</td></tr>
<tr><td>SD</td><td>0.706</td><td>0.643</td><td>0.238</td></tr>
</table>
The estimate of difference of ln transformed data ($\ln X_t$ - $\ln X_r$) is equal to -0.01224 with the 2-sided 95% Confidence Interval [-0.04591, 0.02143].
This is a subset of the interval [-0.223, 0.223], so the equivalence of test with the reference treatment is declared.</td></tr>
<tr><td>Secondary efficacy end points:</td><td>The mean Peak FEV1 values were 2.886 ± 0.715 and 2.788 ± 0.655 for the reference and test formulation respectively. There was no statistical significant difference (p = 0.3669)
FEV1 values over time for the 12 hour observation period were compared at the following time points: 15minutes, 30 minutes, 1-2-4-6-9 and 12 hours. In none of these time points statistical significant difference was observed.
Time to peak FEV1 was 316 minutes and 352 minutes for the reference and test formulation respectively. This difference was not statistically significant (p=0.3295).
None of the three secondary end-points shows any statistically significant difference between the test and the reference product</td></tr>
<tr><td>Safety:</td><td>5 adverse events were recorded in 4/28 patients. None of these</td></tr>
</table>

	AE resulted in discontinuation of the study. There were no deaths. All patients underwent physical examination, 12-lead ECG, blood glucose and serum potassium levels measurements and examination of vital signs. No clinical significant changes were reported between the two formulations
Conclusions	A multicenter, randomized, double blind, double dummy, cross over single dose, therapeutic equivalence study comparing the Test Rolenium Elpenhaler (fluticasone salmeterol 500/50 mcg dpi) with the Reference Seretide Diskus (fluticasone salmeterol 500/50 mcg dpi) was performed in patients with mild to moderate persistent asthma. The Test product (Rolenium ElpenHaler 500/50) produced an equivalent bronchodilator effect compared to the Reference Seretide Diskus 500/50, as demonstrated by the equivalency of the FEV_1 AUC_{0-12}/12h in patients with mild to moderate asthma. In addition no differences were found with respect to the secondary end-points of mean peak FEV1, Time to Peak FEV1 and FEV1 values over time. Both formulations showed equivalent safety profile. The overall results obtained in this trial allow for concluding therapeutic equivalence of the Test with the Reference product.
Date of the report:	29-Aug-2008