Results of the SAM113063 Phase IV Study

Patient population and methodology

20 Hungarian centres participated in the study. Patients were treated with SERETIDE DISKUS powder – containing 50µg salmeterol and 250µg fluticasone propionate. To be eligible to participate in the study male of female patients had to be between the ages of 18 and 70 with clear documentation that the patient has been suffering from asthma for at least 6 months before enrollment. 4 weeks before entering the study patients had to be on a stabil dose of inhaled corticosteroid, a maximum of 800µg budesonide or beclomethazone, or 500 µg fluticasone. At the screen visit the FEV$_1$ value must be >60% of the predicted normal value (short acting beta$_2$ agonists should not be used 6 hours before the test). There should be at least 15% reversibility at screen or a documented test done within 6 months.

The study had two phases, a 2 week run-in phase and an 8 week treatment phase. During the run-in phase patients only received their standard medication with VENTOLIN being used as rescue medication. The use of long lasting beta$_2$ agonists, cromolyns, anti-leukotrienes should be discontinued 2 weeks before randomisation, the use of xantin derivatives, anticholinergs and short lasting beta$_2$ agonists should be discontinued a week before randomisation. Patients should not have received systemic corticosteroids 12 weeks before enrollment, nor should they have been treated in hospital for exacerbation of asthma symptoms. Untreated or instable systemic disease was an exclusion criterium and so was cancer or COPD. Women who were pregnant or lactating could not enter the study, nor could subjects allergic or hypersensitive to the study drug or lactose. Patients with a smoking history must be on less than 10 packs per year.

Subjects who entered the treatment phase received 2 times 50/250µg SERETIDE daily and had to have a FEV$_1$ value of >60% of the predicted normal value and a symptom score of at least 4.

During the course of the study subjects had to fill in a patient’s diary with details of symptom scores, use of VENTOLIN rescue medication and the morning and evening PEF values. There were a total of 4 visits, during each visit Spirometry tests were performed, blood-pressure and pulse rates were checked.

Important parameters

Primary endpoint: The mean change of the morning PEF value compared to the baseline value of the run-in period.

Secondary endpoints:

- Information from the patients diaries – evening PEF values, use of VENTOLIN rescue medication, frequency and severity of symptoms at night and during the day, subjects opinion about the effectiveness of the treatment
- Information recorded during the visits – AEs, number and severity of exacerbations, physical status of the subjects, blood pressure and pulse rate
Statistical Methods

Statistical method for the measurement of PEF: Repeated measurements variance analysis, which can be used to examine changes in the mean PEF. If the time factor is significant, then the mean differences between the baseline and the other visits, and also for the mean differences confidence intervals can be calculated. The confidence interval characterises the mean effect in a given time. Effects of other factors (age, gender, site) were also taken into consideration. To test the effect of age, gender and site a mixed model of ANOVA was applied, with time (weeks) and sex as fix effects, site as a random effect and age as covariate. The covariance structure was verified by the likelihood ratio test. A compound symmetry covariance structure was used. As a result the mean change and the 95% CI was given, adjusting for age, sex and site. We used the baseline morning PEF value of the last seven days of the run-in period.

1. Severity codes were averaged over periods (daytime asthma scores – severity of symptoms)
2. Relative frequencies of days with symptoms
3. Patients with or without symptoms, and also the use of rescue medication (Ventolin)

These summary measures were available for every patient of the ITT population (340 patients). These summary measures were compared by nonparametric tests. Change of severity and frequency between periods was compared by Friedman test, the change from run-in period was compared by Wilcoxon’s matched rand test with Bonferroni correction. The change of presence or absence of symptoms was compared by McNemar test.

Results

372 subjects were enrolled into the study. 350 subjects received study medication, out of these 22 dropped out during the run-in period and 2 patients didn’t fulfill the randomisation criteria. 64.3% (225) of the patients treated with SERETIDE were women and 35.7% (125) were men. 344 subjects completed the study, 6 dropped out. The statistical analysis contains data from the 340 patients with well documented diaries. The mean age was 43.5 (18-69).

Efficacy

The primary endpoint was the mean change of the morning PEF value compared to the baseline value of the run-in period. The morning PEF values significantly increased (p<0.0001) (diagram 1/a).

One secondary endpoint was the change of the evening PEF values. The evening PEF values significantly increased (p<0.0001) (diagram 1/b)

Another secondary endpoint was the change in the severity of the asthma symptoms. One way of demonstrating the severity is by looking at the severity scores calculated from the severity
codes. Compared to the run-in period, during the day and also at night the mean severity scores decreased significantly – diagrams 2/ and 2/b.

Another secondary endpoint was the use of VENTOLIN rescue medication while on SERETIDE. Results show a significant reduction in the use of VENTOLIN rescue medication compared to the run-in period. The number of subjects using VENTOLIN rescue medication during the treatment period also decreased. (Diagram 5)

We also examined the opinion of the doctor and the patient with respect to the efficacy of the treatment. During visits 3 and 4 the efficacy was indicated on a four point scale – highly effective; effective; satisfactory; no effect. The opinion of both the patient and the doctor changed significantly to indicate effectiveness (p<0.0001) (diagram 4).

FEV₁ values were recorded at each visit. The mean FEV₁ values significantly increased with time. The mean difference recorded between the first and last visit was 0.353 litres (p<0.0001) (diagram 5).

**Safety**

276 of the patients did not report any AEs at all. 52 patients had one adverse event, 25 patients reported 2 AEs. A total of 98 AEs were recorded. The 48 AEs of 28 patients could most likely be associated with the use of SERETIDE. The most frequent such event was hoarseness, reported by 14 patients. No SAEs were reported. There were no unscheduled visits as a result of asthma exacerbation. During the 10 weeks there was only one case of an exacerbation, but the patient didn’t require hospitalization.

**Conclusions**

Use of SERETIDE DISKUS powder for the treatment of moderate asthma resulted in a significant improvement in all the endpoints. This includes the PEF, FEV₁ values, the asthma symptom scores and the use of VENTOLIN rescue medication. Adverse events were mild. The doctors and patients gave their opinions about SERETIDE and 324 out of the 340 patients decided to continue using SERETIDE.
Diagrams

Morning PEF values, mean night values

Evening PEF values, mean daytime values
Diagram 2/a

Asthma symptoms severity score - Daytime

Diagram 2/b

Asthma symptoms severity score - Night
5. Table Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 hét kezelés után (3. vizit)</th>
<th>8 hét kezelés után (4. vizit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Morning PEF values L/min</td>
<td>291</td>
<td>340</td>
<td>349</td>
</tr>
<tr>
<td>Mean evening PEF values L/min</td>
<td>285</td>
<td>344</td>
<td>352</td>
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<tr>
<td>Mean symptom score (Night)</td>
<td>0.93</td>
<td>0.48</td>
<td>0.39</td>
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<tr>
<td>Mean symptom score (Daytime)</td>
<td>1.21</td>
<td>0.66</td>
<td>0.51</td>
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<tr>
<td>Mean FEV1 (liter)</td>
<td>2.28</td>
<td>2.64</td>
<td>2.63</td>
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<tr>
<td>Use of VENTOLIN</td>
<td>0.83</td>
<td>0.43</td>
<td>0.35</td>
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<td>Use of VENTOLIN</td>
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</tr>
<tr>
<td>(Night)</td>
<td>1.38</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>(Daytime)</td>
<td>0.51</td>
<td></td>
<td></td>
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</tbody>
</table>

**Literature**

1. Jenkins C, Woolcoock AJ, Saarelainen et al: Salmeterol/fluticasone propionate combination therapy 50/250 μg twice daily is more effective than budesonide 800 μg twice daily in treating moderate to severe asthma. Respir Med 2000; 94, 715-723


7. Bateman ED, Silins V, Bogolubov M: Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100μg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med 2001; 95, 136-146.


10. Ringdal N, Chuchalin A, Chovan L. et al.: Evaluation of different inhaled combination therapies (EDICT) a randomised, double-blinde comparison of Seretide (50/250 microg bd) Diskus vs. Formoterol (12 microg bd) and budesonide (800 microg bd) given concurrantly (both via Turbuhaler) in patients with moderate-to-severe asthma. Respir Med. 2002; 96, 851-61