2. SYNOPSIS

Title of the study:	Impact of two different doses of ciclesonide (160 µg o.d. and 320 µg o.d) administered in the evening on Quality of Life in patients with moderate persistent asthma. A Pilot Study.
Protocol number:	BY9010/ AR101
Investigator(s):	Local Multicenter study
Study Center(s):	11 local study centers
Clinical Phase:	IIIb
Study period:	Study initation date: 14 FEB 2006 Study completion date : 01 MAR 2007 Treatment period: 8 weeks
Objectives:	To study the: • Impact of ciclesonide given in two different dose regimens administered in the evening on QoL in patients with moderate persistent asthma. • Correlation of pulmonary function test with QoL • Time to first asthma exacerbation. • Compliance to treatment, use of rescue medication and adverse events.
Methodology:	Elegible patients (FEV_1 ≥70% and ≤ 90% of predicted values; reversibility ≥ 12% or ≥ 200 mL after inhalation of 400 µg salbutamol) will be enrolled in a baseline period of 2 weeks during which they will be washed out of their basal treatment (ICS dose equivalent of 250 up to 500 µg BDP / day) and will receive only short-acting beta2-agonists as rescue medication. After the end of the baseline period, patients fulfilling randomization criteria (FEV_1 ≥60%-≤ 80% of predicted values) will be assigned to one of the following groups for a treatment period of 8 weeks: • ciclesonide 160 µg ex actuator o.d. in the evening • ciclesonide 320 µg. ex actuator o.d in the evening. Additionally a short-acting beta2-agonists (salbutamol) as rescue medication, as needed. AQLQ(S) will be assessed and lung function parameters FEV_1 and FVC will be measured by spirometry at Visit B0 and T0 and each treatment visit (Visits T2, T4 and T8).. Morning and evening PEF, night and day asthma symptom scores, number of inhalations of rescue medication and time to first exacerbation will be documented in a diary throughout the study. Adverse events will be recorded at every visit of the study. Patients will undergo an oropharyngeal inspection at every visit and oropharyngeal swab will be performed if applicable.
Number of patients: (total and for each treatment):	101 patients in total, 51 patients in ciclesonide 160 µg ex actuator o.d arm and 50 in ciclesonide 320 µg ex actuator o.d. arm.

Diagnosis and criteria for inclusion:	<u>Diagnosis:</u> • Moderate persistent asthma, according to ATS. <u>Inclusion criteria for baseline period:</u> • Written informed consent, • Outpatients of either sex, • Age ≥ 21 to 65 years inclusive • Clinical diagnosis of moderate persistent asthma, i.e. asthma symptoms (e.g. wheezing, cough, breathlessness) daily, and night symptoms more than once per night, but not every night, during the last 6 months prior to visit B0, • Pre-treatment with ICS dose equivalent to 400 - 800 ug BDP / day at stable dosing during the last 4 weeks prior to visit B0, concomitant or not to short-acting beta2-agonists treatment as rescue medication. • FEV_1 ≥70% and ≤ 90% predicted measured at least 4 h after the last use of rescue medication at visit B0, • Reversibility ≥ 12% in B0, B1 or T0 after inhalation of 400 µg of salbutamol. • Good health with the exception of asthma. • Patients complaint to recommended pretreatment
Criteria for exclusion	• Concomitant severe diseases or diseases which are contraindications for the use of inhaled steroids (e.g. active pulmonary tuberculosis or relevant fungal, bacterial or viral infections of the lower respiratory tract demanding specific treatment), • The patient suffers from COPD (i.e. chronic bronchitis or emphysema) and/or other relevant lung diseases causing alternating impairment in pulmonary function, • Clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation, • Pregnancy, breast feeding, intention to become pregnant during the course of the study or lack of safe contraception in pre-menopausal women, • Exacerbation of asthma within 2 months prior to entry into the baseline period, • Use of systemic steroids up to 12 months before entry into the baseline period, • Use of other drugs not allowed and washout times of prohibited drugs cannot be adhered to, • Known or suspected hypersensitivity to ICS or SABAs and/or to the other excipients of the MDIs, • Intolerance to SABAs, • Beginning of immunotherapy within the study period (exception: patients who are undergoing immunotherapy for at least 6 months are eligible provided the regimen remains the same throughout the trial), • Participation in another study within 30 days preceding and during the present study, • Previous enrollment into the current study, • Known or suspected non-compliance, alcohol or drug abuse, • Subjects who are not able to follow the procedures of the study due to e.g. language problems, psychological disorders, • Patients with reversal of sleep pattern (e.g. night shift workers), • Current smokers ≥ 10 pack/years and ex-smokers ≥ 10 pack/years (≥ 2 pipe pack/years).

Randomization criteria	For entry into treatment period patients have to fulfil the following randomization criteria $FEV_1 \geq 60\%$ and $\leq 80\%$ of the predicted values. Reversible obstruction (either $FEV_1 \geq 12\%$and ≥ 200 mL after inhalation of -400 µg of salbutamol or, if during baseline reversibility (at B0, B1 or T0) cannot be achieved, diurnal PEF fluctuation of at least $\geq 15\%$ during at least 3 within 7 days before randomization.
Test product, dose and mode of administration.	Metered dose inhalers (MDIs) with • Ciclesonide 160 µg/dose (ex actuator corresponding to 200 µg ex valve) 2 puff in the evening. • Ciclesonide 80 ug/dose ex actuator corresponding to 100 µg ex valve) 2 puff in the evening.
Duration of treatment:	8 weeks
Reference therapy, dose and mode of administration	N/A
Criteria for evaluation: Efficacy variables: Safety variables:	<u>Variables of primary interest::</u> • Differences in QoL from AQLQ(S) (T8 vs T0) • Differences in FEV_1 and FVC from pulmonary function tests (T8 vs T0) • Time to first asthma exacerbation. <u>Secondary variables:</u> • Percentage of days with asthma control, • Percentage of days with asthma symptoms, • Percentage of nocturnal awakenings due to asthma, • Asthma symptom score (daytime score, nighttime score, total score), • Number of inhalations of rescue medication, • Differences in diurnal PEF fluctuations from patient's diary • Compliance to treatment. • Vital signs, • Laboratory work-up, • Adverse events.
Statistical methods:	The variables of primary interest AQLQ(s), FEV_1 and FVC according to spyrometer were analyzed using an ANCOVA model (analysis of covariance) including treatment, and sex and centers as fixed factors and the baseline value at the randomization visit and age as covariate. The variable of primary interest "time to the first asthma exacerbation" was analyzed by means of the logrank test. The statistics test were made at level 2.5% in one-tailed The ITT analysis was primary for all tests. The secondary variables: PEF from spirometry (T8/Tfinal vs. T0), PEF_{am} and PEF_{pm} from Diary Record Cards (T8/Tfinal vs. T0) were analyzed using the same ANCOVA model defined for the pulmonary variables of primary interest (FEV_1 and FVC). No adjustments for multiplicity were made in this study

Results	The efficacy and safety of ciclesonide was assessed in this multicenter pilot study ,double blind,randomized,two arms,parallel group in patients with moderate persistent asthma. 101 patients were randomized to receive ciclesonide 160 µg (ex actuator) once daily in the evening or 320 µg (ex-actuator) once daily in the evening for 8 weeks. Treatment groups were comparable for all relevant characteristics Both ciclesonide doses (160 µg or 320 µg) inhaled once daily demonstrates efficacy in maintaining lung function and asthma control in adults with persistent asthma previously managed with moderate doses of ICS. The Overall AQLQ change adjusted means (s.e.) for Ciclesonide 320 µg od vs. Ciclesonide 160 µg od were 0.86 (0.152) vs. 0.90 (0.155). No evidence of statistical significant differences between treatment groups was found (p = 0.415). FEV_1 (L) change adjusted means (s.e.) for Ciclesonide 320 µg od vs. Ciclesonide 160 µg od were 0.38 (0.056) vs. 0.25 (0.057). No evidence of statistical significant differences between treatment groups was found (p = 0.154). FVC (L) change adjusted means (s.e.) for Ciclesonide 320 µg od vs. Ciclesonide 160 µg od were 0.19 (0.062) vs. 0.29 (0.065). No evidence of statistical significant differences between treatment groups was found (p = 0.086). Regarding time to first asthma exacerbation ,overall comparison between Survival distributions did not show evidence of statistically significant differences between treatment groups (Log Rank (Mantel- Cox), Chi-square 0.020, 1 d.f., p = 0.886). Correlations between FEV_1(L) and AQLQ Overall mean score at Visit T8/Tfinal show a significant correlation at the 0.05 level (1-tailed) for 320 µg . None of secondary variables show statically difference between treatment groups. Both doses of ciclesonide were well tolerated. There were no significant differences between the two tested doses of ciclesonide with respect to efficacy and safety in this pilot study.