SYNOPSIS

NAME OF COMPANY: Astellas GmbH **NAME OF FINISHED PRODUCT:** **NAME OF ACTIVE INGREDIENT:** Tacrolimus (FK 506)	**INDIVIDUAL STUDY TABLE REFERRING TO PART IVB OF DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title: A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Tacrolimus MDI as Add-on Therapy to ICS and LABA in Moderate to Severe Persistent Asthmatic Patients		
Responsible medical officer: [redacted]		
Investigator(s): Multicentre, 22 centres in Central and Eastern Europe		
Study Centres(s): Germany (9 centres), Romania (5 centres), Ukraine (5 centres), Czech Republic (3 centres)		
Publications: None to date.		
Study period: 19/10/2004 (First Patient First Visit) - 28/07/2005 (Last Patient Last Visit)	**Clinical Phase:** II	
Objectives: The primary objective of this study was to assess the efficacy of tacrolimus MDI as add-on therapy to an inhaled reference corticosteroid (ICS) in combination with a long-acting beta-2-agonist (LABA) in patients with moderate to severe persistent asthma. The tacrolimus dose groups (combined and separate) were compared to the placebo group. The secondary objective was to investigate the efficacy and safety of the two inhaled doses of tacrolimus. In addition, measurements of tacrolimus blood levels in moderate to severe persistent asthmatic patients were planned.		
Methodology: Phase II, randomized, double-blind, placebo controlled study with three parallel groups conducted for 12 week treatment. Basic medication with regular use of ICS and LABA (fluticasone and salmeterol). Rescue medication with as-needed use of salbutamol.		
Number of patients: Planned: Unbalanced randomization, 50 patients in each tacrolimus dose group and 25 patients in the placebo group. Enrolled: 160 patients randomized 151 patients, 59 to 50 µg tacrolimus BID, 62 to 100 µg tacrolimus BID and 30 to placebo. Completed treatment: 142 patients, 54 in the 50 µg tacrolimus BID group, 59 in the 100 µg tacrolimus BID group and 29 in the placebo group.		

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Diagnosis and main criteria for inclusion: Male or female patients between 18 to 70 years of age inclusive. Patients had a diagnosis of asthma for at least 12 months. Patients had to be pre-treated with inhaled corticosteroids and with a long-acting beta-2-agonist for at least 3 months for control of their asthma, and despite this medication not have achieved good asthma control using ICS and LABA. Patients had an FEV_1 of ≥ 50% to 80% of predicted prior to study entry and demonstrate a reversibility of at least 12% in their FEV_1 within 30 minutes of receiving two puffs of a short-acting beta-2-agonist.

Test product, dose and mode of administration: Patients in the 50 µg BID group inhaled two puffs of active medication by one inhaler (25 µg tacrolimus per puff) in the morning and evening for a treatment period of twelve weeks. Patients in the 100 µg BID group inhaled two puffs of active medication by one inhaler (50 µg tacrolimus per puff) in the morning and evening for a treatment period of twelve weeks. Patients in the placebo group (PLA BID) inhaled two puffs of matching placebo (by one inhaler) in the morning and evening for a treatment period of twelve weeks.

All patients were supplied with Seretide (fluticasone combined with salmeterol) as basic medication for regular, twice daily use. Patients inhaled two puffs of this medication in the morning and evening for the run-in period of four weeks and the treatment period of twelve weeks.

All patients were supplied with salbutamol as rescue medication for on-demand use to replace their other short-acting beta-2-agonists.

Lot numbers:

Product	**Lot No.**
Tacrolimus Inhalation Aerosol Placebo	[redacted]
25 µg Tacrolimus Inhalation Aerosol	[redacted]
50 µg Tacrolimus Inhalation Aerosol	[redacted]
Bronchospray Novo (HFA-BDP)	[redacted]
Salmeterol 25 µg/Fluticasone-17-diproprionate 125 µg	[redacted]

Duration of study and treatment: The study duration was twenty weeks. After a 4-week run-in period each patient was treated for twelve weeks with a follow-up visit to occur four weeks after the final dose of study drug.

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Criteria for evaluation: The primary endpoint was the absolute change in patient's maximum value of FEV_1 from baseline (Day 1) to Day 84 / end of treatment.

Multiple secondary endpoints were explored for efficacy:

- % predicted FEV_1, FVC, PEF, $FEF_{25-75\%}$, FEV_1 / FVC; asthma exacerbations, time to first asthma exacerbation, time to withdrawal due to asthma exacerbation

- Patient diary data: AM and PM PEF; beta-2-agonist usage; asthma symptom scores (shortness of breath, chest tightness, wheezing, cough, total score); sleep disturbance score; asthma symptom free days

Secondary endpoints were included for safety:

- Physical examination; - Vital signs; - Adverse events; - ECG; - Haematology; - Blood Chemistry;

Statistical methods: All efficacy analyses were performed on the full analysis set (primary analysis) with supportive analysis on the Per Protocol Set (PPS). The primary objective was to demonstrate a significant superior efficacy of the tacrolimus dose levels compared to placebo as an add-on therapy to an ICS in combination with LABA with respect to the primary efficacy variable defined above. To demonstrate efficacy, predetermined sequential test procedure (First: 50 µg BID + 100 µg BID combined vs. placebo; second: 100 µg BID vs. placebo and 50 µg BID vs. placebo) was applied and the set of null hypotheses was tested by a Wilcoxon rank sum test at the $\alpha = 0.05$ level. For pair wise comparison of the 3 dose groups an analysis of covariance (ANCOVA) model was applied using the treatment as factor and baseline pre-dose FEV_1 as covariate. All secondary lung function variables were analyzed with the same ANCOVA model and using standard descriptive statistics and graphical displays. The incidence rates of asthma exacerbations were analyzed with Fisher's Exact test and the time to first asthma exacerbation as well as the time until withdrawal due to asthma exacerbation with Kaplan-Meier methods. Patient diary data were summarized descriptively.

Safety variables were summarized descriptively by treatment group. Adverse events were coded using MedDRA primary system organ class, preferred term, intensity and relationship to study drug. Treatment groups were compared using Fisher's Exact test. Laboratory data were summarized with descriptive measures by time point and classifications according to the reference ranges were summarized with incidence rates of low and high values by visit and in shift tables. Vital signs, body weight and ECG data were summarized with descriptive measures by time point.

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RESULTS:

Demographics: All patients enrolled into this study were Caucasian. The mean age of enrolled patients was 49.3 years, while slightly more female (55.6%) than male (44.4%) patients were enrolled. Most patients were non-smokers (82.1%) or ex-smokers for more than two years (85.2% of ex-smokers). Mean baseline disease characteristics are summarized below.

	50 µg BID	**100 µg BID**	**Placebo**
FEV_1 (L)	2.05	2.13	2.04
FEV_1 Predicted (%)	65.7	70.0	67.3
FEV_1 Reversibility (%)	25.2	26.2	25.8
Asthma History (years)	16.4	15.4	18.2

Study drug administration: The median duration of treatment was 85 days in all treatment groups. Overall treatment duration ranged between 1 and 105 days.

Efficacy: Significant efficacy of tacrolimus over placebo could not be concluded. The adjusted mean changes from baseline from the ANCOVA were almost equal in all treatment groups, with 0.31 mL in both the 100 µg BID group and the placebo group and 0.30 mL in the 50 µg BID group. The p-value of the Wilcoxon rank sum test comparing the combined tacrolimus treatment groups to the placebo group was 1.000. Results in other pulmonary function parameters were similar.

At least one asthma exacerbation during the treatment phase occurred in 8.5% of patients in the 50 µg BID group, 9.8% of patients in the 100 µg BID group, and 26.7% of patients in the placebo group. The difference between the 50 µg BID group and placebo group was significant (p-value 0.0291, Fisher's Exact test). One patient in the placebo group required oral corticosteroids; 1 patient in the 50 µg group and 1 patient in the 100 µg group were hospitalized due to lung function deterioration.

Diary records related to asthma symptoms included the use of salbutamol, the counting of asthma symptom-free days, sleep disturbance and total asthma symptom scores. Patients tended to record stronger improvements in the tacrolimus groups than those patients in the placebo group.

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RESULTS (continued):

Safety: The highest incidence rates of treatment emergent adverse events was observed in the 100 µg BID group (62.9%), followed by the 50 µg BID group (47.5%) and the placebo group (46.7%). The incidence rates of causally related adverse events were 41.9% in the 100 µg BID group, 23.3% in the placebo group and 18.6% in the 50 µg BID group. One patient (1.7%) in the 50 µg BID group and 4 patients (6.5%) in the 100 µg BID group experienced a total of 6 serious treatment emergent adverse events, but only 1 patient in the 100 µg BID group experienced 2 serious adverse events. One patient from the 50 µg BID group died 19 days post EOT from a non-treatment emergent, non-related, serious adverse event (acute myocardial infarction). The incidence of adverse events leading to withdrawal from study medication was evenly distributed with 3.4% in the 50 µg BID group, 4.8% in the 100 µg BID group and 3.3% in the placebo group.

Median changes from baseline in laboratory data were small and no major differences between the treatment groups were seen. Median values of vital signs and ECG parameters remained stable throughout the study in all treatment groups.

CONCLUSIONS: The (adjusted) absolute change in maximum FEV_1 as well as in the percent change from baseline to last pre-dose measurement during treatment, were comparable across all treatment groups. Compared to the placebo group, the times to first asthma exacerbation were significantly lower in the 50 µg group ($p = 0.0135$) and in the 100 µg group ($p = 0.0425$).

The safety profile of FK506 MDI is consistent with that reported previously and raised no cause for clinical concern.