SYNOPSIS

NAME OF COMPANY: Astellas Europe **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 multicentre, randomized, double-blind, double-dummy, placebo-controlled, parallel-group multiple dose study of the efficacy and safety of tacrolimus inhalation aerosol in patients with moderate persistent asthma		
Responsible medical officer: [redacted]		
Investigator(s): Multicentre, 26 centres in Central and Eastern Europe		
Study Centre(s): Ukraine (8 centres), Hungary (7 centres), Poland (7 centres), Lithuania (4 centres)		
Publications: None to date.		
Study period: 29 September, 2004 (first patient first visit) - 08 June, 2005 (last patient last visit)		**Clinical phase:** II
Objectives: To demonstrate a statistically significant trend across the tacrolimus doses and to determine the efficacy as well as the safety of four different active dose levels of tacrolimus aerosol in comparison to placebo and an inhaled corticosteroid in patients with moderate persistent asthma.		
Methodology: Randomized, double-blind, double-dummy, placebo-controlled, multiple dose study with six parallel groups, four tacrolimus dose groups (12.5 µg BID, 25 µg BID, 50 µg BID, 100 µg BID), placebo, and HFA-BDP as active control.		
Number of patients: Planned: 360 randomized patients, 60 per treatment arm; enrolled: 412 patients; randomized: 384 patients, 63 to 12.5 µg BID, 63 to 25 µg BID, 65 to 50 µg BID, 64 to 100 µg BID, 65 to placebo and 64 to HFA-BDP; completed treatment: 341 patients, 57 on 12.5 µg BID, 57 on 25 µg BID, 56 on 50 µg BID, 59 on 100 µg BID, 52 on placebo, 60 on HFA-BDP		

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Diagnosis and main criteria for inclusion: Patients aged between 18 and 70 years with a diagnosis of moderate persistent asthma for at least 6 months who were steroid naive or without steroids for at least 6 weeks prior to study. Patients had to have an FEV_1 of 60 to 80% of their predicted value, a reversibility of greater than 15% and at least 0.200L increase in their FEV_1 within 15 to 30 minutes of two puffs of a short acting $ß_2$ agonist. Further patients had to use a short-acting $ß_2$ agonist more than two times per day for at least four days per week.

Test product, dose and mode of administration: Metered Dose Inhalers (MDI) of tacrolimus aerosol were supplied in four strengths of 0.0125% aerosol (6.25 µg tacrolimus/puff), 0.025% aerosol (12.5 µg/puff), 0.05% (25 µg/puff), and 0.1% (50 µg/puff). HFA-BDP was supplied as extra fine aerosol containing 100 µg/puff and two placebos matching both tacrolimus and HFA-BDP. For each study drug two puffs had to be taken upon each administration and they were administered twice daily. Since tacrolimus and HFA-BDP inhalers were different the double dummy technique was used to ensure blinding (e.g. a patient randomized to 12.5 µg BID took two puffs of the 0.0125% aerosol inhaler and two puffs out of the HFA-BDP matching placebo inhaler both in the morning and in the evening). Study medication had to be inhaled prior to the meals and after inhalation the mouth had to be rinsed with water.

Lot numbers:

Product	**Lot No.**
Tacrolimus Inhalation Aerosol Placebo	[redacted]
6.25 µg Tacrolimus Inhalation Aerosol	[redacted]
12.5 µg Tacrolimus Inhalation Aerosol	[redacted]
25 µg Tacrolimus Inhalation Aerosol	[redacted]
50 µg Tacrolimus Inhalation Aerosol	[redacted]
Junik Dosieraerosol 100 µg (tacrolimus placebo)	[redacted]
Bronchospray Novo (HFA-BDP)	[redacted]
HFA-BDP Placebo 200 Dose Aerosol	[redacted]

Duration of study and treatment: Patients had a 1 to 2-week run-in phase, followed by a 12-week treatment phase and follow-up visit 4-weeks after the end of the treatment phase.

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Criteria for evaluation: Primary efficacy endpoint was the change from baseline to the end of treatment (Week 12) in maximum FEV_1. Secondary efficacy endpoints included % predicted FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, PEF, asthma exacerbations, time until withdrawal due to asthma exacerbation; patient diary data: morning and evening PEF, $ß_2$ agonist (= rescue medication) usage, asthma symptom scores, (wheezing, shortness of breath, chest tightness, cough, total score), sleep disturbance score, asthma symptom-free days.

Safety endpoints were adverse events, clinical laboratory data, vital signs, and ECG data.

Statistical methods: All efficacy analyses were performed on the full analysis set (primary analysis) with supportive analysis on the Per Protocol Set. The primary objective was to demonstrate a significant trend over the tacrolimus dose levels with respect to the primary efficacy variable defined above. To demonstrate a trend over the dose levels a step-down closed test procedure was applied and the set of null hypotheses was tested by the Jonckheere-Terpstra procedure at the $\alpha = 0.025$ level. To compare the tacrolimus dose levels with placebo and 200 µg HFA-BDP an analysis of covariance (ANCOVA) model using the treatment as factor and baseline pre-dose FEV_1 as covariate was applied. 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 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 (AEs) were summarized by MedDRA, version 6.0 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 references 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: The patients enrolled into this study were predominantly young to middle-aged adults (mean of 44 years), primarily female (64.1%) and of Caucasian race. The vast majority of patients were non-smokers (89%) and only one patient reported excessive alcohol consumption. Mean baseline disease characteristics are summarized in the following overview.

	12.5µg BID	25µg BID	50µg BID	100µg BID	Placebo	HFA-BDP
FEV_1 (L)	2.37	2.43	2.36	2.34	2.36	2.18
FEV_1 Predicted (%)	74.9	73.5	74.8	74.4	74.8	74.4
FEV_1 Reversibility (%)	27.2	28.8	26.9	28.4	27.2	28.4
Asthma History (years)	6.5	7.2	6.8	5.9	7.6	7.5

Study drug administration: The duration of treatment was in the median 85 days, in all treatment groups. Overall treatment duration ranged between 2 and 96 days.

Efficacy: The adjusted mean change from baseline was most pronounced in the 25 µg BID dose group (0.28L), followed by the 12.5 µg BID dose group (0.25 L) and the 50 µg BID and 100 µg BID dose groups (both 0.18 L). Thus, none of the null hypotheses using the closed test procedure for the trend problem could be rejected and a dose-response relationship for the four different tacrolimus doses employed in this study could not be shown. The adjusted mean change from baseline in the placebo group was 0.13L and in the HFA-BDP group an adjusted mean change from baseline of 0.32L was observed. Apart from the treatment contrast HFA-BDP versus placebo there were no statistically significant differences between the treatment groups. Results for all other lung function parameters were similar.

The incidence of asthma exacerbations and in particular asthma exacerbations assessed as being causally related to study drug was low. Overall, 21 patients in the Full Analysis Set had an asthma exacerbation during the treatment period or within 7 days after the last dose, for 10 patients these asthma exacerbations were assessed as being causally related to study drug. All of these patients except one patient in the 50 µg BID group were withdrawn from the study prematurely, as required by the study protocol. Most commonly asthma exacerbations occurred in the placebo group (6 patients, 9.4%) and the 50 µg BID group (5 patients, 7.8%).

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RESULTS (continued):

Safety: About half of the patients in the 50 µg BID group (47.7%), the 100 µg BID group (51.6%), the HFA-BDP group (50.0%), and the placebo group (50.8%) had at least one treatment emergent adverse event whereas overall adverse event incidence rates were somewhat smaller in the 25 µg BID group (38.1%) and the 12.5 µg BID group (44.4%). Adverse events considered by the investigators to be causally related were evenly distributed over the treatment groups and ranged between 25.0% (HFA-BDP) and 30.8% (50 µg BID). Incidences of adverse events, including asthma exacerbation, leading to withdrawal from treatment were lowest in the HFA-BDP group (2 patients) and highest in the placebo group (9 patients). Overall, the most frequently reported adverse events were throat irritation reported for 27 patients, nasopharyngitis (23 patients), and asthma (22 patients).

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 primary endpoint of this study, based on changes from baseline FEV_1, was inconclusive regarding the presence or absence of efficacy for tacrolimus. Overall, efficacy data were consistent in showing little difference relative to the placebo group, whereas the active control (beclomethasone) group did show a modest lung function improvement. All study drug dosages were safe and well tolerated.