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| **NAME OF COMPANY:**<br>Astellas Pharma GmbH<br><br>**NAME OF FINISHED PRODUCT:**<br><br>**NAME OF ACTIVE INGREDIENT:**<br>Tacrolimus (FK506) | **INDIVIDUAL STUDY TABLE REFERRING TO PART IVB OF DOSSIER**<br>**Volume:**<br><br>**Page:** | **(FOR NATIONAL AUTHORITY USE ONLY)** |
| **Title:** A Multicentre, Randomized, Double-blind, Double-dummy, Parallel-group Study Investigating the Efficacy and Safety of Three Different Doses of Tacrolimus Inhalation Aerosol and a Standard Dose of Inhaled Corticosteroid (ICS) in Patients with Moderate Persistent Asthma | | |
| **Responsible medical officer:** [redacted] | | |
| **Investigator(s):** Multicentre, 50 centres in Central and Eastern Europe. | | |
| **Study Centre(s):** Bulgaria (5 centres), Czech Republic (3 centres), Germany (15 centres), Hungary (5 centres), Poland (8 centres), Russia (8 centres) and Ukraine (6 centres) | | |
| **Publications:** None to-date | | |
| **Study period:** 20 October 2004 (first patient, first visit) to 26 August 2005 (last patient, last visit). | **Clinical phase:** Phase II | |
| **Objectives:** To demonstrate a statistically significant trend across the tacrolimus doses and to determine the efficacy as well as the safety and tolerability of three different doses of tacrolimus inhalation aerosol in comparison to a standard dose of an inhaled corticosteroid in patients with moderate persistent asthma being pre-treated with inhaled corticosteroids. | | |
| **Methodology:** Randomized, double-blind, double-dummy, active-drug controlled, multicentre, parallel group study with three different tacrolimus dose levels (25, 50 or 100 µg BID) in comparison with a standard dose of an inhaled corticosteroid (200 µg HFA-beclomethasone, referred to as HFA-BDP). | | |
| **Number of patients:** Planned: 320 randomized patients, 80 per treatment arm; considering a drop-out rate of about 10% in the screening period 360 patients were planned for enrolment.<br><br>Randomized: 370 patients, 91 to 25 µg BID, 95 to 50 µg BID, 96 to 100 µg BID, and 88 to HFA-BDP; completed treatment: 329 patients, 78 on 25 µg BID, 85 on 50 µg BID, 86 on 100 µg BID, and 80 on HFA-BDP. | | |

**Diagnosis and main criteria for inclusion:** Patients aged between 18 and 70 years with a diagnosis of asthma for at least 6 months. Patients had to be pre-treated with inhaled corticosteroids for at least 6 months prior to study entry and use a short acting ß2-agonist more than twice a day for at least 4 days per week. Patients had to have a $FEV_1 \geq$ 60 to 80% of the predicted value, a reversibility of at least 15% and at least a 200 mL increase in their $FEV_1$ within 30 minutes of receiving two puffs of a short acting ß2-agonist.

**Test product, dose and mode of administration:** Metered Dose Inhalers (MDI) of tacrolimus aerosol were supplied in three strengths: 0.025% aerosol (12.5 µg tacrolimus/puff), 0.05% aerosol (25 µg tacrolimus/puff) and 0.1% aerosol (50 µg tacrolimus/puff). MDIs of HFA-BDP were supplied as aerosol (100 µg HFA-BDP/puff). MDIs of tacrolimus matching placebo and of HFA-BDP matching placebo were supplied. For each study drug two puffs were 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 25 µg BID group took two puffs of the 0.025% aerosol and two puffs of the HFA-BDP matching placebo inhaler both in the morning and the evening). Study medication had to be inhaled prior to meals and after inhalation the mouth was to be rinsed with water.

**Lot numbers:**

| Product | Lot No. |
|---|---|
| Tacrolimus inhalation aerosol placebo | [redacted] |
| 12.5 µg tacrolimus inhalation aerosol | [redacted] |
| 25 µg tacrolimus inhalation aerosol | [redacted] |
| 50 µg tacrolimus inhalation aerosol | [redacted] |
| Bronchospray novo (HFA-BDP) | [redacted] |
| Junik beclomethasone 100 µg | [redacted] |
| Junik placebo (beclomethasone 0 µg) | [redacted] |

**Duration of study and treatment:** Patients had a 4-week initial run-in period, followed by a 12-week treatment phase and a 4-week follow-up period.

**Criteria for evaluation**: The 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 first asthma exacerbation and time until withdrawal due to asthma exacerbation; patient diary data: morning and evening PEF, $ß_2$ agonist usage (rescue medication), asthma symptom scores (wheezing, shortness of breath, chest tightness, cough, total score), sleep disturbance score, and 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 across the tacrolimus dose levels with respect to the primary efficacy variable. To demonstrate a trend across the dose levels a step-down closed test procedure was applied and the set of null hypotheses was tested by the Jonckheere-Terpstra procedure (1-sided) at the $a = 0.025$ level. To compare the tacrolimus dose levels with 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 first asthma exacerbation and until withdrawal due to asthma exacerbation with Kaplan-Meier methods and a log-rank test. Patient diary data were summarized descriptively. Adverse events were summarized by MedDRA primary system organ class, preferred term, intensity and relationship to study drug. Differences between treatment groups in adverse event incidence rates were analyzed by 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 including changes from pre-dose and changes from baseline.

**RESULTS**:

**Demographics:** The patients enrolled into this study were predominantly middle-aged adults (mean of 46.4 years), primarily female (53.5%) and of Caucasian race. The majority of patients were non-smokers (83%). Mean (SD) baseline disease characteristics for the Safety Analysis Set are summarized in the following overview.

| | **Tacrolimus** | | | |
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| | **25 µg BID N=91** | **50 µg BID N=95** | **100 µg BID N=96** | **HFA-BDP N=88** |
| **$FEV_1$ (L)** | 2.23 (0.56) | 2.23 (0.55) | 2.36 (0.58) | 2.27 (0.61) |
| **$FEV_1$ % predicted** | 72.4 (5.7) | 70.6 (7.0) | 70.8 (6.6) | 72.8 (5.9) |
| **$FEV_1$ reversibility (%)** | 26.3 (12.8) | 27.3 (10.2) | 24.6 (8.3) | 25.6 (8.7) |
| **Asthma history (years)** | 11.6 (9.2) | 11.8 (11.2) | 9.9 (8.9) | 12.1 (11.7) |

**Study drug administration:** The median duration of treatment was 85 days in all treatment groups. Overall treatment duration ranged between 1 and 120 days.

**RESULTS (CONTINUED)**:

**Efficacy:** For the Full Analysis Set the adjusted mean change from baseline in $FEV_1$ maximum value was almost identical in all three tacrolimus dose groups, i.e. 0.16 L in the 25 µg BID dose group, 0.17 L in the 50 µg BID dose group, and 0.18 L in the 100 µg BID dose groups. Thus, none of the null hypotheses using the closed test procedure for trend assessment could be rejected and a dose-response relationship could not be shown. The adjusted mean change from baseline in the HFA-BDP group was 0.25 L. There were no statistically significant differences between any two treatment groups. Results for the Per Protocol Set and the other lung function parameters were similar.

The incidence of asthma exacerbations during double-blind treatment and within 7 days thereafter was similar across all treatment groups (range 16.1% to 20.8%). All asthma exacerbations were also reported as adverse events. Incidence rates of asthma exacerbations considered to be causally related to study drug were similar in all treatment groups. No statistically significant difference between any two treatment groups in the incidence of asthma exacerbations was seen. Kaplan-Meier estimates for the time until first asthma exacerbation and for the time until withdrawal due to asthma exacerbation showed no trend with regard to earlier or later withdrawal in any group.

**RESULTS (CONTINUED)**:

**Safety:** Approximately half of the patients in all treatment groups had at least one treatment emergent adverse event, with incidences being similar across groups.

Adverse events considered by the investigators to be causally related to study drug were most frequent in the 50 µg BID group (29.5%) and less frequent in the other three treatment groups (20.9% in the 25 µg BID group, 22.9% in the 100 µg BID group and 19.3% in the HFA-BDP group). Two patients in the 25 µg BID group, 1 patient in the 50 µg BID group and 4 patients in the HFA-BDP group experienced at least one serious adverse event; no patients in the 100 µg BID group experienced a serious adverse event. No serious adverse event was considered to be causally related to study drug by the Investigator. Incidences of adverse events leading to withdrawal from treatment, including asthma exacerbation, were lowest in the HFA-BDP group (2 patients) and highest in the 50 µg BID and 100 µg BID groups (7 patients each).

Overall, the most frequent adverse event in all four treatment groups was asthma reported for 15 patients (16.5%) randomized to 25 µg BID, 18 patients (18.9%) randomized to 50 µg BID, 21 patients (21.9%) to 100 µg BID and 13 patients (14.8%) randomized to HFA-BDP. The preferred term "asthma" also included asthma exacerbations/deteriorations. Other frequently reported adverse events were throat irritation (8.8% in the 25 µg BID group, 9.5% in the 50 µg BID group, 7.3% in the 100 µg BID group and 6.8% in the HFA-BDP group) and nasopharyngitis. The only statistically significant difference observed between treatment groups was for the incidence rate of nasopharyngitis between the HFA-BDP group (8.0%) and the 50 µg BID group (1.1%, p=0.0295); incidences of 2.2% and 4.2% were observed for the 25 µg BID and 100 µg BID groups.

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 $FEV_1$ maximum value 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 HFA-BDP active control group, the changes in $FEV_1$ in the tacrolimus groups were slightly smaller. The small, non-significant difference observed was consistent with the numbers of exacerbations as well as with patient diary data: symptom score, sleep disturbance score, puffs of salbutamol taken for symptom relief and gain in symptom-free days.

The safety profile of FK506 MDI is consistent with that reported previously and raised no cause for concern. FK506 MDI was safe and well tolerated in patients with moderate persistent asthma.

Whole blood concentrations were linear and demonstrated large inter-individual variability.