Clinical Study Synopsis

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<td>Budesonide</td>
<td>Page</td>
<td>04-9214</td>
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Title: Clinical Trial of High-Dose Steroid (Budesonide) Inhalation Treatment of Patients with Cystic Fibrosis and Chronic Pseudomonas Aeruginosa Lung Infection.

Investigators: Christian Koch, MD PhD; Niels Haiby, MD PhD; Hans Bisgaard, MD PhD; Eva Mosfeldt Laursen, MD; Kim Nielsen, MD; and Marianne Skov, MD.

Study Centre: Danish Cystic Fibrosis Centre, Copenhagen, Department of Paediatrics, National University Hospital, DK-2100 Copenhagen Ø.

Publications: None.


Clinical Phase: III

Objectives: To investigate whether inhalation of a high dose of steroid can improve the clinical condition, primarily the lung function, in patients with cystic fibrosis (CF) and chronic broncho-pulmonary Pseudomonas (P.) aeruginosa infection.

Study Design: Prospective, randomized, double-blind, single-centre, parallel group comparison of budesonide inhalation via Turbuhaler® and matching placebo. The study consisted of: 1) a 2-week run-in phase and 2) a 6½-month double-blind comparative phase. Patients received three 2-week treatment courses with systemic antipseudomonal antibiotics.
starting at month -\( \frac{1}{2} \), month 3, and month 6, respectively.

Number of Patients: Planned: 90 patients, 45 in either treatment group. Randomized: 33 patients (budesonide) and 31 patients (placebo). Analyzed (All Patients Treated Approach): 30 patients (budesonide) and 25 patients (placebo). There were 25 males and 30 females, aged between 9 and 29 years.

Diagnosis and Criteria for Inclusion: Patients of either sex \( \geq 8 \) years of age with CF and chronic (\( \geq 1 \) year) broncho-pulmonary P. aeruginosa infection.

Investigational Product: Budesonide inhalation (Pulmicort® Turbuhaler®, Astra Draco AB, Lund, Sweden) 800 µg in the morning and 800 µg in the evening.

Reference Therapy: Matching placebo (manufactured by Astra Draco AB, Lund, Sweden) inhaled morning and evening.

Duration of Treatment: 6\( \frac{1}{2} \) months.

Assessment Methods: Primary efficacy end-points: Forced Vital Capacity (FVC) and Forced Expiratory Volume_{1 second} (FEV_{1}) measured at each clinic visit. Secondary efficacy end-points: 1) FVC and FEV_{1} measured by patients themselves and recorded in a Diary; 2) maximum fall in FEV_{1} during a physical exercise test, and 3) PC_{20} (histamine) (i.e. concentration of inhaled histamine that reduces FEV_{1} by 20%). The physical exercise test and determination of PC_{20} (histamine) were performed during the 1st and 3rd antibiotic treatment courses. Safety: Monitoring of adverse events and measurement of plasma immunochemistry and haematology and plasma chemistry variables.

Statistical Methods: All analyses were carried out using the All Patients Treated Approach. For each variable the last available value was used for the main comparison according to the Last Value Extended Principle. Means, SDs, and ranges for patient
Baseline characteristics were tabulated by treatment group. Primary and secondary efficacy endpoints were analyzed for within-group changes and between-group differences using Student’s paired and unpaired t-tests, respectively. All tests were 2-sided. 95% confidence intervals for changes and differences were calculated. Frequency counts of adverse events were tabulated as were summary statistics for laboratory variables.

Summary of Results:

FVC remained unchanged at 3.5 ± 1.25 L (mean ± SD; n=29) (month 0) and 3.5 ± 1.19 L (n=29) (month 6) in the budesonide group and fell from 3.0 ± 1.16 L (n=24) (month 0) to 2.9 ± 1.12 L (n=24) (month 6) among patients assigned to placebo. The between-group difference at 6 months (i.e., budesonide - placebo) was 0.069 L (95% confidence interval [-0.161; 0.300]; p=0.567). FEV₁ remained unchanged at 2.2 ± 0.90 L (n=29) (month 0) and 2.2 ± 0.91 L (n=29) (month 6) in the budesonide group and fell from 2.1 ± 1.08 L (n=24) (month 0) to 2.0 ± 1.02 L (n=24) (month 6) among patients assigned to placebo, corresponding to an approximately 5% deterioration in the placebo group. The between-group difference at 6 months was 0.100 L (95% confidence interval [-0.048; 0.248]; p=0.201). The study failed to show any effect on lung function variables recorded in the Diary or on exercise induced fall in FEV₁. There was a borderline statistically significant increase of 1.150 mg/mL in PC20 (histamine) (from 5.3 at month 0) among budesonide treated patients as compared to an increase of 0.017 mg/mL (from 4.9 at month 0) in the placebo group (p=0.048).

A total of 14 adverse events (AEs) were reported by 12 budesonide treated patients and 10 AEs were reported by seven patients in the placebo group. The two most common AEs in both groups were dysphonia and mouth/throat moniliasis. No serious AEs considered to be drug-related occurred. No change was observed in laboratory variables measured to monitor safety.

Conclusion(s):

The present study was dimensioned to detect a 15% difference between inhaled budesonide and placebo in terms of effect on FVC. The effect on FVC actually observed - in a representative group of patients - was in the order of 2% in favour of
budesonide. Lung function, as assessed from FEV₁, remained unchanged in the budesonide group and deteriorated by approximately 5% among patients assigned to placebo. This effect was statistically non-significant, but is relevant from a clinical point of view. Fewer patients than planned were included in the study. To permit definite conclusions to be drawn regarding effect of inhaled budesonide on lung function, a larger study would be needed. Short-term treatment with inhaled budesonide was found to be safe and well tolerated.