# SYNOPSIS

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| ***Name of Sponsor/Company:*** EDMOND PHARMA Srl Italy | |
| ***Name of Active ingredient*** Erdosteine | |
| ***Title of Study***: The efficacy and safety of erdosteine in the long term therapy of Chronic Obstructive Pulmonary Disease (COPD). A 12-month, randomised, double blind, placebo-controlled, parallel group, multicenter, study ERD-01-08/EP | |
| ***Pricipal Investigtors:*** Prof. R. Dal Negro – **Study Coordinator,** Ospedale Civile "Orlandi", Bussolengo (VR) - Italy<br>***Total number of Centers:*** 55 centres), | |
| ***Study period (years)***:<br>First enrolment: November 2009<br>Last completed: February 20014 | ***Phase of development***<br><br>Phase III |
| ***Objectives*** The primary objective of the study was to evaluate the efficacy of erdosteine, compared to placebo, in reducing the number of acute exacerbations over a 12-month treatment period in patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II-III COPD. The secondary objectives of the study was to investigate the effects of erdosteine on pulmonary function parameters, clinical symptoms and quality of life, and to assess the long-term safety of the drug. | |
| ***Methodology***: Prospective, multinational, multicenter, randomised, group-parallel double-blind, placebo-controlled trial. | |
| ***Number of patients analysed:*** analysed 467. | |
| ***Diagnosis and main criteria for inclusion:***<br>- Outpatients of both sexes, aged between 40 and 80 years.<br>- Diagnosis of COPD (Stage II and III according to GOLD 2007)<br>as follows:<br>• post-bronchodilator FEV1/FVC ratio < 70%<br>• post-bronchodilator 30% ≤ FEV1 ≤ 70% predicted (and at least 0.7 L absolute value)<br>- Current or past smokers (smoking history of ≥ 10 pack-years)<br>- On a stable therapeutic regimen for COPD for at least 8 weeks prior to inclusion, and maintaining the same regimen during the study period in the absence of clinical reasons for a change<br>- Having experienced at least 2 acute exacerbations of COPD requiring medical intervention within 2-12 months prior to inclusion<br>- Presence of chronic COPD symptoms (cough, sputum production, dyspnoea)<br>- Having a mean cough and sputum score (derived from BCSS) of at least 1.5 for each symptom during run-in<br>- Having a chest x-ray consistent with a diagnosis of COPD and performed no more than 1 year before the screening visit.<br>- Willing and able to comply with study procedures<br>- Written informed consent to participate | |
| ***Test product, dose and mode of administration, batch number:*** – Erdosteine 300 mg, 1 cps. b.i.d. batch number: ERC30210509/002409001 and ERC30170311/ERC30010111 | |
| ***Duration of treatment:*** The active treatment period was 12 months. In addition, there was be a 2-week run-in period. | |
| ***Reference therapy, dose and mode of administration, batch number:*** None (placebo controlled trial). | |

***Criteria for evaluation***:

Primary endpoint

Number of acute COPD exacerbations occurring in the two treatment groups during the 12-month treatment period. COPD exacerbations are defined as a symptomatic worsening requiring treatment with antibiotics, systemic corticosteroids, or both.

Main Secondary endpoints

1. Time to first exacerbation
2. Number of hospitalizations due to COPD exacerbations
3. Morning pre-dose FEV1, FVC, FEF25-75% at each clinical visit
4. COPD symptom scores (BCSS scale)
5. Use of "reliever" medication
6. Subject's and Physician's global assessment of Disease Severity

***Statistical methods***:

Sample size

The sample size has been calculated according to a multiplicative intensity (MI) model as described by

Andersen and Gill for comparison of two treatment groups, based on the following assumptions:

- two-tailed test
- % reduction (i.e. estimated % size of the difference between the effect of treatments on the primary

efficacy parameter): 20% average number of exacerbation: 1.3 per patient

- 1st type error: 0.05
- 2nd type error: 0.20

Primary efficacy analysis

The statistical analysis on primary outcome has been simplified to detect major trends in efficacy and safety as multivariate analysis would have been affected by over-fitting.

The coprimary variable of frequency of exacerbations per patient per year was analyzed nonparametrically using the Wilcoxon rank sum test.

A predefined analysis of exacerbation frequency was performed using a Poisson regression model, with the covariates of treatment, age, sex, Body Mass Index, and FEV1 at the baseline to estimate the rate ratio. The natural logarithm of the duration, expressed as months in the study, was used as an offset variable to correct for differences in the time individuals spent under observation. Rate ratios from this model are expressed as percent reductions.

Results should have been reported as a risk ratio for an exacerbation in the treatment versus the placebo group. A risk ratio less than 1 thus indicates a protective effect of treatment. The outcomes data were sampled (Intention to Treat ITT Population). For all patients the time of every exacerbation has been recorded. Patients has been censored at the time they drop out of the study or do not have any further exacerbation.

Time to exacerbation was calculated as the time from the beginning of the study to the first exacerbation for the first exacerbation, and as the difference between the times of two consecutive exacerbations for subsequent occurrences. For patients who finish the study, the last day of the study was the last follow-up time; for those who drop out, their drop-out date has been the last follow-up date. Results was reported as a risk ratio for an exacerbation in the treatment versus the placebo group. A risk ratio less than one thus indicates a protective effect of treatment.

Secondary efficacy analyses

For use of "reliever" medication, the median data during the 12-month study period has been analysed using the Wilcoxon rank-sum test.

After normality testing (Kolmogorov-Smirnov test) and eventual log-transformation for normalization purpose, pulmonary function parameters, BCSS and QoL scores, distance (meters) walked in the 6MWT have been submitted to an ANCOVA model with treatment and centre (country) as factors, and baseline (V2) as a covariate.

Time to first exacerbation, which compares the number of patients with acute exacerbation in a survival analysis framework has been evaluated by the log-rank test and described by Kaplan Meier method.

Further adequate tests have been carried out to improve the interpretation of the observed trends.

We coded adverse events according to the Medical Dictionary for Regulatory Activities (MedDRA). The proportion of patients presenting adverse events (AE), adverse events leading to withdrawal, adverse drug reactions and serious adverse events have been tabulated for each treatment group.

The distribution over time of the clinical laboratory parameters have been analysed describing and comparing frequencies of abnormal values at baseline and after 12 months of treatment by means of Mc Nemar Test.

Comparisons within treatment has been performed by calculating the 95% CI of the changes from baseline, when applicable.

***SUMMARY – CONCLUSION***

*EFFICACY RESULTS*:

After 1 year of treatment the total number of all exacerbations recorded was 457; 196 (42.9%) exacerbations in erdosteine group versus 261 (57.1%) in the placebo treated group.

In the study population the rate of all exacerbations per patient per year was significantly lower in the erdosteine group compared to placebo (-17.1%; erdosteine 0.91 vs. placebo 1.13/patient/yr; p=0.01). Fewer episodes were reported with erdosteine as derived from the Poisson model. This result was driven by the reduction of mild exacerbations rate per patient per year (-57.1%; erdosteine 0.23 vs placebo 0,54/patient/year; p=0.002).

91 patients treated with erdosteine and 70 treated with placebo did not experience a single exacerbation episode during the trial, with a relative risk of 0.8291 (P=0.01) in favour of erdosteine.

The proportion of patients being exacerbation-free at the end of one year, significant in favour of erdosteine (P=0.009).

The mean duration of exacerbations was significantly shorter in the erdosteine group (-24.4 ± 3.1%) compared to the placebo group, with 9.55 days (SD 15.6) in the erdosteine group and 12.63 days (SD 18.7) in the placebo group (mean difference: -3.08 ± 1.64, 95% CI, P= 0.023) .

Time to first exacerbation was 122.9±109.9 days in the erdosteine treated group and 112.3±103.4 days in the placebo treated one (p= 0.452).

Subject's Global Assessment of Disease Severity was significantly lower in erdosteine treated subjects compared to patients treated with placebo (1.48 ± 0.74 vs. 1.65 ± 0.74, mean difference = -0.167, 95%CI, P= 0.022).

Physician's Global Assessment of Disease Severity was significantly lower in erdosteine treated subjects than in placebo ones: 1.53 ± 0.73 vs. 1.68 ± 0.80, mean difference = -0.149 (95%CI from -0.297 to -0.001, P= 0.048).

The SGRQ trend is for reduction of all sub-score and total score across all visits, but between group score difference is not significant.

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| The use of “reliever” medication (inhaled long acting bronchodilators, ICS and short-acting inhaled β2-agonists) was allowed during the study period, and carefully registered by the patients on a daily basis (by diary).<br>Only 10.2% of erdosteine treated patients versus 33.7% of patients treated with placebo needed to increase reliever medication during the trial (Fisher exact test P<0.001).<br>Lung function was assessed by FEV1, FVC, FEF25-75% and the encouraged 6MWT, with no differences being observed between active treatment and placebo.<br>The hospitalizations due to COPD exacerbations in the study was low, 5.7% of erdosteine treated patients and the 7.2% of the patients treated with placebo experienced hospitalization due to COPD exacerbations. |
| *SAFETY RESULTS*:<br>The observed serious adverse events were similarly distributed per number and severity between the treatment groups. Three not drug related deaths have been recorded during the entire study period.<br>Most serious adverse events were single cases and hardly stackable by organ or apparatus so that no specific evaluation has been carried out. Overall the safety profile of erdosteine seems to be identical to the one of placebo. |