**Supplementary Material**

# Effect of erdosteine on the rate and duration of COPD exacerbations: the RESTORE study

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## Methods

Study design

The 10 countries in which sites were located were: Belgium, Bulgaria, Czech Republic, Denmark, France, Italy, Poland, Romania, Slovakia, United Kingdom.
Before the randomisation there was a 2-week run-in period during which patients continued their usual COPD therapy and the stability of patient clinical condition and COPD symptoms (cough and sputum) were recorded. At the subsequent six visits has been assessed the occurrence and duration of any COPD exacerbations, the use of reliever medications identified from the patient diary card, the pulmonary the pre-dose $FEV_1$, FVC, and any reported adverse events. The St. George's Respiratory Questionnaire (SGRQ) was administered at baseline and month 6 and 12 together with the Patient's and Physician's Global Assessments. Twelve-lead ECG and routine blood/urine analysis were conducted at screening and at study end.

Study subjects

**BASELINE CHARACTERISTICS OF PATIENTS WHO COMPLETED OR DID NOT COMPLETED THE TRIAL**

| | Patients completing the trial | | Drop-out | |
|---|---|---|---|---|
| | Erdosteine | Placebo | Erdosteine | Placebo |
| Age. Yr | 63.8 (8.3) | 64.1 (8.2) | 65.1 (8.5) | 65.5 (8.9) |
| Male sex. n (%) | 71.8 | 74.6 | 73.1 | 75.2 |
| BMI (kg/m2) | 27.2 (5.3) | 28.0 (5.4) | 27.4 (5.4) | 27.9 (5.9) |
| Smoking status | | | | |
| - Current smokers (%) | 27.1 | 28.0 | 29.6 | 28.8 |
| - Ex-smokers (%) | 72.9 | 72.0 | 70.4 | 71.2 |
| $FEV_1$ Absolute Value (L) | 1.43 (0.40) | 1.46 (0.47) | 1.36 (0.38) | 1.43 (0.41) |
| $FEV_1$ % Predicted (L) | 51.45 (12.8) | 54.38 (13.3) | 51.36 (11.2) | 50.34 (11.7) |
| FVC (L) | 0.74 (0.93) | 2.74 (0.94) | 2.74 (0.71) | 2.73 (0.73) |
| Post bronchodilator.FEV1/FVC ratio | 54.01 (11.3) | 53.26 (10.8) | 51.88 (11.1) | 52.39 (10.1) |
| $FEF_{25/75\%}$ (L) | 0.63 (0.36) | 2.64 (22.12) | 0.58 (0.33) | 2.28 (25.9) |

**Inclusion Criteria:**

1. Outpatients of both sexes, aged between 40 and 80 years
2. Diagnosis of COPD (Stage II and III according to GOLD 2007) as follows :
    - Stage II Moderate – $FEV_1/FVC < 70\%$; $50\% \leq FEV_1 < 70\%$
    - Stage III Severe – $FEV_1/FVC < 70\%$; $30\% \leq FEV_1 < 50\%$
3. Current or past cigarette smokers with a history of smoking of at least 10 pack-years
4. 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
5. Having experienced at least 2 acute exacerbations of COPD requiring medical intervention within 2-12 months prior to inclusion
6. Presence of chronic COPD symptoms (cough, sputum production, dyspnoea)
7. Having a mean cough and sputum score (derived from BCSS) of at least 1.5 for each symptom during run-in
8. Having a chest x-ray consistent with a diagnosis of COPD and performed no more than 1 year before the baseline visit
9. Willing and able to comply with study procedures
10. Written informed consent to participate

**Exclusion Criteria:**

1. Female subjects: pregnant, lactating mother or lack of efficient contraception in a subject with child-bearing potential (i.e. contraceptive methods other than oral contraceptives, IUD, tubal ligature)
2. Acute exacerbation of COPD within 8 weeks prior to inclusion
3. Treatment with antibiotics and/or systemic steroids and/or hospitalisations within 8 weeks prior to inclusion
4. Change of the therapeutic regimen for COPD in the last 8 weeks prior to inclusion
5. COPD stage IV
6. Current or past diagnosis of asthma
7. A $FEV_1$ reversibility test showing $\Delta FEV_1$ of morethan 400 ml, 30 minutes after inhalation of 400 µg of salbutamol pMDI
8. Clinically significant or unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; significant hepatic impairment; significant pulmonary disease (e.g. tuberculosis, bronchiectasis, cystic fibrosis, lung cancer); cardiovascular disease (e.g. coronary artery disease, uncontrolled hypertension, evidence of heart failure NYHA class III-IV); gastrointestinal disease; neurological disease; haematological disease; autoimmune disorders, or others
9. Significant renal impairment as indicated by creatinine clearance < 25 ml/ min
10. Active peptic ulcer
11. Subjects with liver cirrhosis as well as patients with cystathionine-synthetase deficiency are excluded from participating in the study due to the possible interference of erdosteine metabolites with methionine metabolism, in line with contraindications reported in SmPC
12. Long term oxygen therapy
13. Known or suspected hypersensitivity to erdosteine
14. Participation in another clinical trial with an investigational drug within 60 days prior to inclusion

**Outcomes**

Health Related Quality of Life was assessed at baseline and after 6 and 12 months of treatment through the St. George's Respiratory Questionnaire (SGRQ) a validated 76-item questionnaire developed to measure health in chronic airflow limitation.
A total score was calculated from the individual scores of the three components (symptoms, activity and impact on daily life), with lower scores corresponding to better health status. A change of $\geq 4$ units has been reported to indicate the minimal clinically important difference relevant to the patient[1].

The Six Minutes Walk Test (6MWT) has been carried out at baseline and after 12 months of treatment following standardized procedures, according to ATS guidelines[2]. The test was performed indoors along a long, flat, straight, 30m-long corridor, and one well-trained researcher supervising the test. Prior to starting to walk, patients were told that the aim of the test is to walk from end to end along the corridor and to cover as much distance as possible in the period of 6 minutes. During the 6MWT, subjects was permitted to rest, but encouraged to proceed with the walk when they had recovered. The total distance walked (in meters) was recorded in the relevant section of the CRF as a secondary efficacy parameter.
Subject's and Physician's Global Assessment of Disease Severity was assessed at baseline and after 6 and 12 months of treatment, subjects were asked: "Overall, on a scale 0-4, how troublesome is your lung problem today?"

Responses was graded on the following scale: 0 = not troublesome at all; 1 = a little troublesome; 2 = moderately troublesome; 3 = very troublesome; 4 = unbearably troublesome. At the same visits, Investigators were asked to respond to the following question: "Based on clinical examination and patient interview, how would you rate patient's COPD?" Responses were graded on the following scale: 0 = subject with stable COPD, none or minimal symptoms; 1 = subject with stable COPD, occasional symptoms, fully functional; 2 = subject with stable COPD, recurring symptoms, slight functional impact; 3 = subject with stable COPD, frequent moderate to severe symptoms, functionality limited; 4 = subject with stable COPD, constant severe symptoms, functional impairment

A COPD exacerbation was defined as a symptomatic worsening beyond normal day-to-day variation and requiring a change in regular medication and/or health care resources utilisation (e.g. increased use of bronchodilators, treatment with antibiotics and/or systemic corticosteroids, visit to an emergency department, hospitalization) (3).

The recognition of COPD exacerbations first relied on the recording done by the patients in the paper diary card.

Patients were asked to annotate any change that occurred in their COPD disease, including symptom worsening, increased use of "reliever" medication or need for additional COPD treatment.
The occurrence of an acute exacerbation was registered by the Investigator in the CRF during the clinic visits, recording both the worsened symptoms and the required medical intervention, based on information contained in the diary card (see above). The diagnosis of acute exacerbation could also be formulated retrospectively by the Investigator during each visits, if there was evidence of the patients having sought additional healthcare due to worsening of their clinical conditions.

**Patient's Diary COPD score**

| **Difficulty in breathing** | **Cough** | **Trouble for sputum** |
|---|---|---|
| *How much difficulty did you have breathing today?* | *How was your cough today?* | *How much trouble was your sputum today?* |
| NONE:<br>unaware of any difficulty | NONE:<br>unaware of coughing | NONE:<br>unaware of any difficulty |
| MILD:<br>noticeable during strenuous activity (e.g. running) | RARE:<br>cough now and then | MILD:<br>rarely caused problem |
| MODERATE:<br>noticeable during light activity (e.g. bed making | OCCASIONAL:<br>less than hourly | MODERATE:<br>noticeable as a problem |
| MARKED:<br>noticeable when washing and dressing | FREQUENT:<br>one or more times an hour | MARKED:<br>caused a great deal of inconvenience |
| SEVERE:<br>almost constant, present even when resting | ALMOST CONSTANT:<br>never free of cough or need to cough | SEVERE:<br>an almost constant problem |

## Patient's Diary daily card (example)

**Day 1** |___|___|
dd mm

| *Difficulty in breathing* | *Cough* | *Trouble with sputum* |
|---|---|---|
| ❑ None | ❑ None | ❑ None |
| ❑ Mild | ❑ Rare | ❑ Mild |
| ❑ Moderate | ❑ Occasional | ❑ Moderate |
| ❑ Marked | ❑ Frequent | ❑ Marked |
| ❑ Severe | ❑ Almost constant | ❑ Severe |

*Have you taken your "reliever" medication*?

❑ No ❑ Yes ➔ how many times? |___|___|

## Patient's Diary weekly card (example)

Please answer these simple questions on your COPD disease during the week just elapsed.

| | |
|---|---|
| ☐ **I needed to use my "reliever" medication more usual**<br>How many days ? |___|___|<br>How many times/day ? |___|___| | ☐ **One or more of my respiratory symptoms have become worse**<br>➔ Please tick which one(s)<br>❑ Cough ❑ Shortness of breath<br>❑ Increased volume of sputum ❑ Change of colour in sputum |
| ☐ **I had an extra-medical visit**<br>➔ Please tick which one(s)<br>❑ GP ❑ Lung physician<br>❑ Hospitalisation ❑ Emergency room | ☐ **I have been prescribed additional drugs for COPD**<br>Which ones ? _____<br>_____ |
| ☐ **None of the above** | |

**SERIOUS ADVERSE EVENTS TREATMENT RELATED**

**(Reported by Investigators)**

| SERIOUS ADVERSE EVENTS | ERDOSTEINE | PLACEBO |
|---|---|---|
| **Cardiac Disorders** | | |
| Atrial fibrillation | | |
| Subjects affected | 1 | 0 |
| **Hepatobiliary disorders** | | |
| Gall bladder empyema | | |
| Subjects affected | 0 | 1 |
| **Total subjects** | 1 | 1 |

| NON-SERIOUS ADVERSE EVENTS | ERDOSTEINE | PLACEBO |
|---|---|---|
| **General disorders and administration site conditions** | | |
| Liver function test abnormal | | |
| Subject affected | 1 | 1 |
| Insomnia | | |
| Subject affected | 0 | 1 |
| **Gastrointestinal disorders** | | |
| Gastric ulcer | | |
| Subject affected | 1 | 0 |
| Acidosis | | |
| Subject affected | 0 | 1 |
| Nausea | | |
| Subject affected | 0 | 1 |
| **Hepatobiliary disorders** | | |
| Salivary hypersecretion | | |
| Subject affected | 0 | 1 |
| **Total subjects** | 2 | 5 |

## Methodology references


1. Jones P, Quirk FH et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis **145**:1321-1327, 1992
2. ATS Statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med **166**:111-117, 2002
3. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. Chest. 2000 May;**11**7(5 Suppl 2):398S-401S.


## Contributors

RWDN, PMAC and MI were involved in study design
RWDN and GF were involved in recruiting patients and collecting data
AFC and EP were involved in statistical analysis and data interpretation
RWDN, PMAC, CP, JAW GF and MI contributed in data interpretation and critical review of the report

## Conflict of interest

EP is employed by Edmond Pharma. MI, GF, CP, PMAC, RWDN and AFC report personal fees from Edmond Pharma during the conduct of the study; JAW declare no conflict of interest.


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