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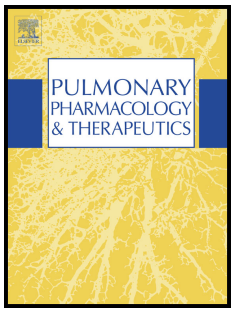


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# The therapeutic efficacy of erdosteine in the treatment of chronic obstructive bronchitis: a meta-analysis of individual patient data

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**Abstract**

Erdosteine, a drug approved for the treatment of acute and chronic pulmonary diseases, has been shown to be an effective treatment for chronic bronchitis or COPD (CB/COPD) in several studies, although marked differences in the perception of its usefulness still remain.

*Aim*: to test the available evidence for the efficacy of erdosteine in adults with stable or exacerbated CB/COPD.

*Methods*: meta-analysis of individual patient data from both published and unpublished randomised controlled trials (RCTs) comparing erdosteine with placebo/mucolytics, given for up to 10 days in association with standard therapy (RCTs used for regulatory drug approval). Individual patient data were provided by the manufacturer of erdosteine, Edmond Pharma (Milano, Italy). Endpoints were symptom scores (cough frequency and intensity, sputum viscosity and purulence, difficulty to expectorate, catarrh rhonchi at auscultation, dyspnoea), a cumulative global efficacy index (cGEI), and an overall physician efficacy assessment (OA).

*Results*: individual data from 1046 patients from 15 RCTs (12 on exacerbated and 3 on stable CB/COPD) were obtained. Erdosteine induced a significant reduction of cGEI *vs*. comparators (-1.02; 95% CI: from -1.60 to -0.44; p = 0.0006), both placebo and mucolytics. On individual symptoms, it positively impacted on cough frequency (-0.19; 95% CI: from -0.34 to -0.03) and intensity (-0.30; 95%CI: from -0.44 to -0.17), sputum viscosity (-0.28; 95%CI: from -0.49 to -0.07), difficulty to expectorate (-0.24; 95%CI: from -0.40 to -0.08), and catarrh ronchi at auscultation (-0.35; 95%CI: from -0.60 to -0.10). The effects on dyspnoea were only significant *vs*. placebo, whereas sputum purulence was not significantly modified. The OA also favoured erdosteine, doubling the chance of success compared with placebo and mucolytics: OR (odds ratio) 2.06; (95%CI: from 1.27 to 3.33). The treatment with erdosteine was well tolerated. Adverse events, mainly gastrointestinal, were reported by 10.2% of patients compared to 11.0% in the reference groups.

*Conclusions*: Treatment with erdosteine is associated with a significant benefit in terms of symptom amelioration both *vs*. placebo and mucolytics in patients with CB/COPD. Although with some limitations (e.g. not fully validated scores) this review reinforces the use of erdosteine, in combination with standard therapy, in respiratory diseases characterized by increased expectoration, namely acute CB/COPD exacerbations.

**Keywords**

Meta-analysis, chronic bronchitis, COPD, acute exacerbation, cough, expectoration.

## Introduction

Chronic bronchitis (CB) is very often associated with airflow obstruction and is especially frequent in smokers, is considered to contribute to the airway mucus hypersecretory component of Chronic Obstructive Pulmonary Disease (COPD) [1], and is associated with considerable morbidity and high health-care costs [2]. Patients with chronic bronchitis and COPD suffer from recurrent exacerbations, with an increase in volume and/or purulence of sputum, cough and dyspnoea which contribute to progressive clinical deterioration and account for a significant proportion of the cost of caring for such patients [3,4,5].

There is evidence for inflammatory and morphological changes in the airways associated with loss of ciliary function and mucus gland hyperplasia, and the importance of mucus in contributing to airflow limitation and disease progression are underscored by recent studies [6,7].

The use of mucolytics as adjunctive treatment of both stable and exacerbated CB/COPD has been proposed to improve disease outcome, although the value of the use of such drugs is still considered uncertain [8].

Erdosteine is a a drug approved for the treatment of acute and chronic pulmonary diseases for more than 10 years which has been shown to improve sputum rheology in patients with mucus hypersecretion through an active metabolite (Met-I) having free thiol groups [9]. Although a few studies have been published showing that CB/COPD patients may benefit from erdosteine, marked differences in the perception of its usefulness still remain.

The aim of the present systematic review is therefore to test the available evidence that erdosteine treatment in patients with CB/COPD may be effective and accompanied by clinically relevant improvements.

## Methods

This systematic review was performed in accordance with the Quality of Reporting of meta-analyses (QUORUM) guidelines [10].

**Types of studies**

Randomized controlled trials (RCTs) focusing on the comparison between erdosteine and placebo or mucolytics which reported data on efficacy and safety after 7-10 days of treatment, were used for this meta-analysis.

**Types of patients**

Adults patients having a medical history of chronic bronchitis (CB), generally defined as the presence of cough and sputum production for at least three months a year over two consecutive years were included in the studies used in this meta-analysis. The three largest studies also included evidence for airway obstruction, defined as an $FEV_1$/FVC ratio at least 10% below the normal theoretical value [11,12,13].

Patients were enrolled either at occurrence of an acute exacerbation or during the stable phase of the disease. The diagnosis of acute exacerbations was based on the occurrence of increased mucopurulent sputum, cough and fever. Three studies additionally included the isolation of antibiotic-sensitive bacterial strains in sputum [11,14,15]. In two studies the inclusion of patients with hypersecretory acute bronchitis was also allowed [15,16].

**Type of intervention**

Erdosteine (300 mg capsule) was administered two or three times daily on top of background therapy, generally antibiotics and bronchodilators ($beta_2$-agonists and aminophyllines) in patients with acute exacerbations, and bronchodilators in those with stable disease.

Placebo or mucolytics (ambroxol, N-acetylcysteine, carbocysteine, sobrerol) were administered with the same dosing schedules as erdosteine (i.e. two or three times daily) on top of background treatments.

**Type of outcome measures**

The following outcomes were investigated: i) cumulative global efficacy index (cGEI), the sum of all assessed respiratory symptom scores, ii) respiratory individual symptom scores (cough frequency and intensity, sputum viscosity and purulence, difficulty to expectorate, catarrh rhonchi at auscultation, dyspnoea), iii) overall assessment of efficacy (OA) by the Investigator, and

frequency of adverse events. In the original studies, similar scoring systems were used for patient self-assessment of symptoms, usually categorised on a 0-3 scale from 0= absent to 3= worst.

In particular: *cough frequency* 1= sporadic fits/mild/occasional, 2= repeated diurnal fits/ moderate/frequent, 3= repeated diurnal and sleep disturbed/severe/continuous; *cough intensity* 1= mild/not disturbing, 2= moderate/fairly disturbing, 3= severe/severely disturbing; *sputum viscosity* 1= fluid almost watery, 2= moderately viscous, 3= viscous & thick; *sputum purulence* 1= mucoid whitish, 2= mucopurulent yellowish, 3= purulent intensely yellow; *difficulty to expectorate* 1= sometimes/easy at first cough fit/mild, 2= often/with some effort/moderate, 3= always/with considerable effort/severe; *catarrh ronchi at auscultation* 1= mild, 2= moderate, 3= severe/remarkable; *dyspnoea* 1= at fast walk/with moderate exertion, 2= at regular walk/with minimal exertion, 3= at slightest effort/at rest. Categories were considered comparable.

In one study [12], the symptoms of cough frequency and intensity, difficulty to expectorate and dyspnoea were assessed on a 5-point scale.

The Investigator's OA was based on 0-3 scale, with 0= none/poor, 1= fair/modest, 2= good, 3= excellent/return to normality. In three studies [16,17,18] efficacy was judged as negative, doubtful or positive, and in one study [12] a 5-point scale was used (none, poor, moderate, good, excellent).

In all the studies, safety was evaluated in terms of incidence of adverse events reported during treatment, with particular regard to gastrointestinal complaints.

**Study Search**

Literature was search systematically for relevant clinical trials with no language restrictions (Pub Med, Google Scholar and Scirus with search terms "chronic bronchitis", "COPD" and "acute exacerbations" combined with "erdosteine"). Furthermore, the manufacturer of erdosteine (Edmond Pharma s.r.l., Italy) was contacted and asked for any additional non-indexed publications and relevant unpublished studies. Individual patient data from the published and

unpublished studies in patients with CB submitted for European marketing approval in 2005 were considered.

**Data extraction**

For each of the selected trials, the following information was retrieved: first author, publication year, details of study design, studied treatments (type of drug, schedule, duration), patient characteristics (total number, age and sex distribution, number randomised and number included in the analysis), study endpoints, occurrence and type of adverse events.

The quality of the selected trials was assessed according to a five-point validated scale [19] measuring a range of factors that impact the quality of a trial: randomization methods, blinding and description of withdrawals and drop-outs. Two independent reviewers assessed the quality of the trials to be included. Differences in the evaluation were resolved by consensus, referring back to the original article/report.

**Statistical analysis**

Trials were grouped according to the type of erdosteine comparator (active or placebo), study quality (Jadad scale score 1-2 *vs*. 3-4-5) and whether the study was published or not.

The summary measure for the respiratory individual symptom scores, as well as for the c-GEI, was the difference between changes from baseline and the end of treatment mean values calculated in the two treatment arms.

For comparison of OA of the efficacy of erdosteine versus active or placebo group, events of interest were considered under the categories good, excellent or positive.

Global estimates of the effect of treatments over time on the selected outcomes and the corresponding 95% confidence intervals (CIs) were calculated using the inverse variance method for continuous variables and the Mantel-Haenszel method for dichotomous variables.

For the pooling of the estimates, either the fixed-effect or the random-effect model were considered, depending on the presence of statistical

heterogeneity. Statistical heterogeneity was defined as an $I^2$ statistic value >50% [20]. In order to assess the heterogeneity of the included trials, the Cochrane Q statistic [21] was calculated. For p-values <0.10, the assumption of homogeneity was deemed not valid.

Occurrence of adverse events was analysed descriptively.

All statistical analyses were made using SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA) and the software 'REVMAN 4.2' provided by the Cochrane Collaboration.

## Results

### *Study selection*

Thirty-one potentially relevant studies conducted in patients with CB/COPD were retrieved. The study selection process is presented in Fig. 1. Of these, 16 were excluded for the following reasons: 3 because they only evaluated mucus rheology [22,23,24], 2 because they were dose-range finding studies [25,26], 5 because of inadequate design [27,28,29,30,31], 3 because of lack of symptom assessment up to 10 days [32,33,34], 1 because of a different formulation of erdosteine [35] and 2 because of insufficient efficacy information [36,37]. Therefore, 15 RCTs were included in the final analysis.

### *Study characteristics*

The main characteristics of the 15 selected RCTs which enrolled 1046 adult patients are summarized in Table 1.

Six studies involving 587 patients were randomized, double-blind trials comparing erdosteine vs. placebo, four studies were performed in patients with acute exacerbations of CB/COPD and two in patients with stable chronic obstructive bronchitis. Erdosteine 300 mg or placebo were administered two or three times daily on top of background therapy. Nine RCTs involving 459 patients compared erdosteine to other mucolytics (ambroxol, N-acetylcysteine, carbocysteine, sobrerol), six studies were double-blinded and three single-blinded. The majority of patients presented with acute CB/COPD exacerbations, and study treatments were administered in association with antibiotics and bronchodilator therapy (beta$_2$-agonists and aminophylline).

Dosing schedules were two or three times daily for both erdosteine and active comparators. Most of the RCTs included a mixed population of both inpatients and outpatients.

### *Study quality*

We characterized the studies according to a set of factors that reflect their methodological rigor. Overall, most studies were considered of good quality in that they were prospective, randomized, double-blind trials. Only 2 [14,16] were not randomized and 3 [16,18,38] were single-blind studies. When applicable, the reasons for early withdrawal were adequately described.

Table 2 summarizes the results of the study quality assessment.

### *Patient characteristics*

The majority of subjects (70.7%) had a diagnosis of acute exacerbation of CB/COPD with a few cases (3.3%) where features of asthma were also present. Patients with stable COPD disease accounted for 26.3% of the study population, while in a negligible proportion of subjects (2.9%) no unequivocal diagnosis of CB/COPD was reported. Rather a hypersecretory pulmonary disease (either acute bronchitis or pneumonia or restrictive lung disease). In patients with exacerbated disease concomitant antibiotics were administered, and 37% of patients received bronchodilator therapy. Use of corticosteroids was very limited. Smoking history was incompletely recorded, and lung function at inclusion was measured in all but 4 studies (72% of patients).

Information related to the patients included in the eligible RCTs is presented in Table 3.

*Outcomes*

In the 1046 patients included in the analysis, erdosteine induced a significant reduction of cGEI versus comparators (-1.02; 95% CI: from -1.60 to -0.44; p = 0.0006). A higher effect was observed in comparison to placebo (-1.41; 95% CI: from -2.49 to -0.33; p = 0.01), although the reduction was also significant vs. active comparators (-0.66; 95% CI: from -1.30 to -0.02; p = 0.04) (Fig. 2).

Data on cough frequency and intensity were available in 13 and 11 RCTs, respectively (972 and 496 participants). Erdosteine positively impacted on cough frequency overall (-0.19; 95% CI: from -0.34 to -0.03; p = 0.02) and achieved significance *vs*. placebo (-0.23; 95%CI: from -0.47 to 0.00; p = 0.05) (Fig. 3). With regard to cough intensity, the effect of erdosteine was significant overall (-0.30; 95% CI: from -0.44 to -0.17; p < 0.00001), vs. placebo (-0.42; 95% CI: from -0.75 to -0.08; p = 0.01) and mucolytics (-0.26; 95% CI: from -0.43 to -0.10; p = 0.002). Data regarding sputum viscosity and purulence were reported in 8 and 12 RCTs, respectively (812 and 946 participants). Erdosteine positively impacted on sputum viscosity overall (-0.28; 95% CI: from -0.49 to -0.07; p = 0.008) and *vs*. placebo (-0.27; 95% CI: from -0.51 to -0.03; p = 0.03), but not on sputum purulence (-0.11; 95% CI: from -0.28 to 0.07; p = 0.25). Data on expectoration difficulty were available in 13 RCTs involving 992 patients. Erdosteine significantly improved this symptom overall (-0.24; 95% CI: from -0.40 to -0.08; p = 0.004) and *vs*. mucolytics (-0.19; 95% CI: from -0.34 to -0.03; p = 0.02) with nearly significant difference being achieved *vs*. placebo (-0.29; 95% CI: from -0.60 to 0.03; p = 0.07), as presented in Fig. 4. The symptoms of catarrh ronchi at auscultation and dyspnoea were evaluated in 8 and 6 RCTs, respectively, involving 469 and 744 patients. The presence of catarrh ronchi at auscultation was significantly reduced by erdosteine (-0.35; 95% CI: from -0.60 to -0.10; p = 0.006), while the effects on dyspnoea were only significant *vs*. placebo (-0.17; 95% CI: from -0.30 to -0.05).
Outcome data related to individual respiratory symptom scores are shown in Table 4.

Data regarding treatment success, defined as physician OA equal to good/excellent/positive, were reported in 13 RCTs. The efficacy of treatment was considered as good/excellent/positive in 297 of 472 patients treated with erdosteine and in 239 of 465 patients treated with comparators. Erdosteine provided a double chance of treatment success compared with placebo and mucolytics (OR 2.06; 95% CI: from 1.27 to 3.33 overall) (Fig. 5).

Statistical analyses did not suggest potential bias either for study quality and for whether a study was published or not (data not shown).

*Safety profile*

All treatments were well tolerated. Adverse events were reported by 54 patients (10.2%) in the erdosteine group and in 57 patients (11.0%) in the reference groups. The most frequently occurring adverse events were gastrointestinal complaints, in particular nausea, epigastric pain or heartburn, diarrhoea or loose stool. Only one patient treated with erdosteine reported taste loss, and allergic reactions occurred in 3 patients treated with erdosteine and in 3 with reference treatments. A summary of reported adverse events is presented in Table 5.

## Discussion

The present systematic review on erdosteine efficacy has been conducted on individual patient data obtained in 15 both published and unpublished studies, selected from a dossier used for recent European registration by the manufacturing company and consistent with the clinical indication object of this meta-analysis, with the evaluation of a total of 1046 patients. Although a company-driven bias in the retrieval of the studies cannot be definitively ruled out and the overall number of patients was rather small, there are several positive features in the present work that support the validity of the observed findings. The direct access to individual patients' data and the possibility to include unpublished studies in our view have contributed to reduce the publication bias that sometimes may represent a limit of systematic reviews based on published data. Additionally, the methodology of meta-analysis can overcome a lack of power of single individual trials, as it was the case especially for the unpublished studies. In this respect, the sensitivity analysis performed to evaluate possible heterogeneity due to publication and/or study quality did not show significant differences.

The results of the present meta-analysis, conducted on studies focusing on the comparison between erdosteine and placebo or mucolytics, indicate that the addition of erdosteine to background treatment of patients with

CB/COPD can be beneficial with significant effects observed in the overall population included, both patients with acute infective exacerbations and with stable disease. A significantly better outcome was demonstrated in patients treated with erdosteine for the cumulative index of global efficacy and for each of the individual symptoms, except for sputum purulence and dyspnoea, and reflected by the significantly higher percentage of treatment success, as indicated by the physician's final efficacy assessment.

The advantage provided by erdosteine was especially evident *versus* placebo. Since in these studies the majority of patients (namely those with acute respiratory infections) were treated with antibiotics, it derives that erdosteine combined with an antibiotic treatment is therapeutically more useful than antibiotic monotherapy [11,14,15,39]. The index of global efficacy and the physician's OA, when available, significantly favoured erdosteine in all of the studies. The individual symptom scores related to cough and expectoration, including the more objective assessment of catarrh ronchi at auscultation in two studies [11,40], indicated a faster amelioration of this symptom during the 7-10 days of treatment in the patients also receiving erdosteine.

When considering the two studies conducted in patients with stable CB/COPD [12,40], the benefit provided by erdosteine on cough and sputum scores was less evident, presumably due to the short duration of treatment in these studies. It should be noted however, that in another study, not considered for the present review, a more prolonged treatment of 28 days significantly improved chronic symptoms of cough and sputum in stable CB patients [33]. In the comparative studies *vs*. placebo, a significant effect on dyspnoea was also shown, suggesting that a facilitated mucus clearance with erdosteine has the potential to translate into improved quality of life for patients with CB. On the other hand, erdosteine was no more active on sputum purulence scores compared to antibiotic monotherapy, a finding that is perhaps not surprising given the major efficacy of antibiotics on this feature of exacerbations, rather than mucolytics.

These results underline the potential relevance of interventions focused on mucus clearance for the treatment of CB and COPD. While smoking cessation, bronchodilators, glucocorticosteroids and antibiotics (especially for acute exacerbation of CB) provide an effective armamentarium for the treatment of the symptomatic and airflow abnormalities of CB/COPD in all phases of the disease, the mucus component of airway obstruction has generally received less attention than other reversible compounds of the condition [8]. Nonetheless, if mucus can be effectively cleared, both symptoms and airflow may be relevantly improved, given that sputum is also a reversible component of the disease. In this respect, recent studies have raised renewed interest in the relevance of mucus in airway diseases and the role of mucolytic-expectorant treatments as an additional therapeutic strategy in the treatment of CB/COPD [7].

The present findings indicate that erdosteine plus antibiotics is more effective than antibiotic monotherapy in patients with CB/COPD, especially for the treatment of acute infective exacerbations, and support the addition of erdosteine to the usual treatment in order to provide further resolution of symptoms and allow a more rapid recovery.

Alternative mucolytic treatments with proven efficacy in patients with CB are available [41,42]. In the present meta-analysis, the comparison *versus* other active mucolytics given at comparable doses and regimens (either bid or tid), provided evidence of a tendency to erdosteine having a better efficacy. This evidence was prevalently obtained in patients suffering from acute exacerbations of CB which represented the vast majority of the study population *versus* active comparators used in the present meta-analysis [13,17,43,44,45,46]. Taking each symptom individually, a general trend in favour of erdosteine was observed, except for sputum purulence and dyspnoea, and this translated into a significant reduction of the cumulative global efficacy score and a higher percentage of treatment success in patients treated with erdosteine. The more pronounced effect of erdosteine may be suggestive of a more rapid onset of activity, this being a feature already reported to characterize erdosteine pharmacologically [17,47,48].

Mucolytic therapy has often been overlooked because of the difficulty of demonstrating effectiveness by objective criteria, the presence of clinical data that were sometimes contradictory, and uncertainty about the type of patients likely to benefit from their use.

In this respect, possible drawbacks of the studies considered for this meta-analysis should be addressed. In the studies used in the present meta-analysis, respiratory symptoms have been subjectively assessed on Likert-type 0-4 scales (none to severe/almost constant). Although not fully validated, these scales are comparable to scoring systems employed in studies performed in similar patient populations when evaluating the effects of other therapeutic interventions, such as bronchodilators and/or inhaled corticosteroids ICSs [49,50,51]. Although the patient's self-reporting on symptoms is regarded as an important measure to monitor disease activity and outcomes of care, a subjective symptom assessment may imply an incorrect estimate of treatment effectiveness and be unrelated to more objective measurements of disease improvement. The lack of a validated method to assess symptoms severity may therefore weaken the findings of the present review. It should be noted, however, that relatively few instruments are available in this respect, The more recent Breathlessness, Cough and Sputum Scale (BCSS), proposed as a reliable and responsive method for symptom monitoring [52], was not available at the time when the studies used in this meta-analysis were conducted; nevertheless it should be advisable to evaluate once more the symptomatic benefits provided by erdosteine through validated scoring methods to obtain more robust evidence for efficacy. Another possible limitation may be related to the concomitant treatments administered to the patients, namely the scarce intake of ICSs. Background treatments were mainly bronchodilators ($beta_2$-agonists and theophylline) with antibiotics when patients were suffering from acute exacerbations. Since the most recent surveys report use of ICSs in a vast proportion of COPD patients in Europe, the present findings need to be confirmed in patients also receiving corticosteroids in order to ensure their generalization to the today's patient population and to assess the added

value that erdosteine (or other mucolytic treatments) may confer on top of already administered anti-inflammatory treatments. However there is no reason to disregard the possibility of a positive interaction between anti-inflammatory and expectorant interventions. Furthermore, it should be remembered that bronchodilators are the recommended therapy for CB/COPD until the severe stages, and that the use of antibiotics represent the mainstay treatment for acute infective exacerbations. There is therefore still a not negligible number of CB/COPD patients who could certainly benefit from the addition of erdosteine to their usual therapy, as shown by the present results.

In conclusion, the present meta-analysis supports the effectiveness of erdosteine in patients with CB/COPD, especially during acute exacerbations, and provides further strength to the published ACCP guidelines recommending the use of erdosteine on a short-term basis to increase mucous clearance [53]. Furthermore appropriately sized studies with fully validated endpoints should be undertaken to reinforce the present results and better define the longer-term benefit of erdosteine in patients with CB/COPD.

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# Figures

**Figure 1**
Flow diagram of study selection

Footnote:
CB chronic bronchitis. RCTs randomized controlled trials. Eu MA European Marketing Authorization

**Figure 2**
Comparison of erdosteine *versus* placebo and other mucolytics.
Outcome: Cumulative Global Efficacy Index (cGEI)

**Figure 3**
Comparison of erdosteine *versus* placebo and other mucolytics.
Outcome: Cough frequency

**Figure 4**
Comparison of erdosteine *versus* placebo and other mucolytics.
Outcome: Difficulty to expectorate

**Figure 5**
Treatment success in patients treated with erdosteine *versus* placebo and other mucolytics.

**Figure 1**

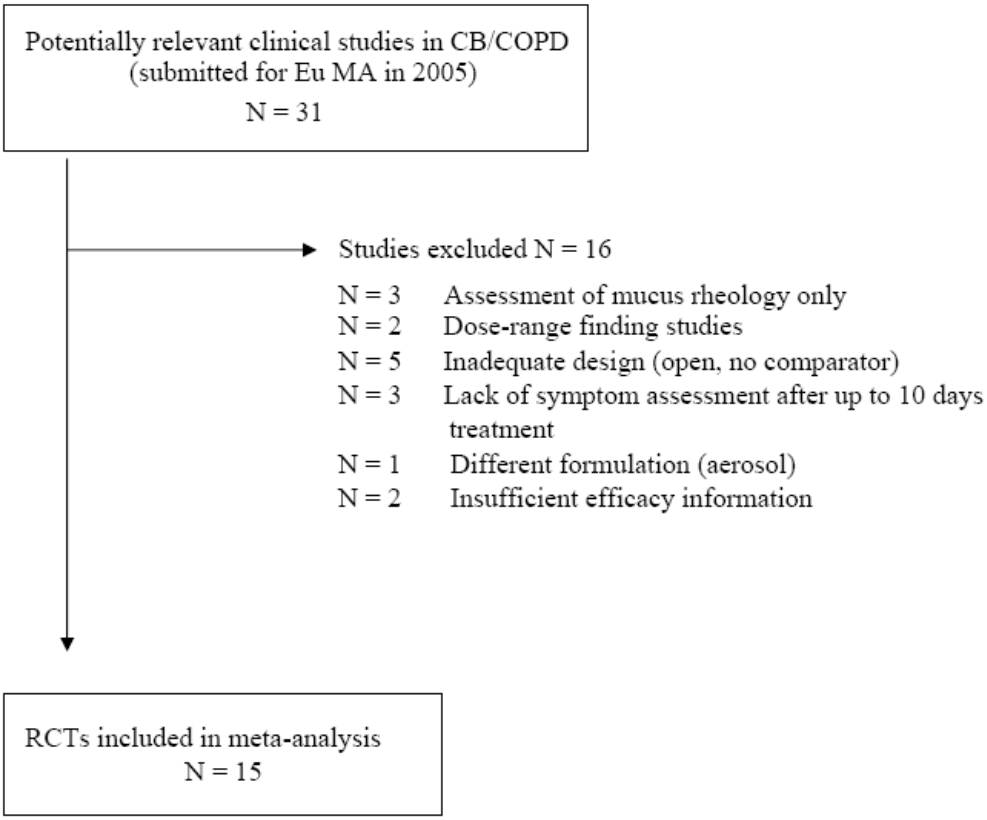


**Figure 2**

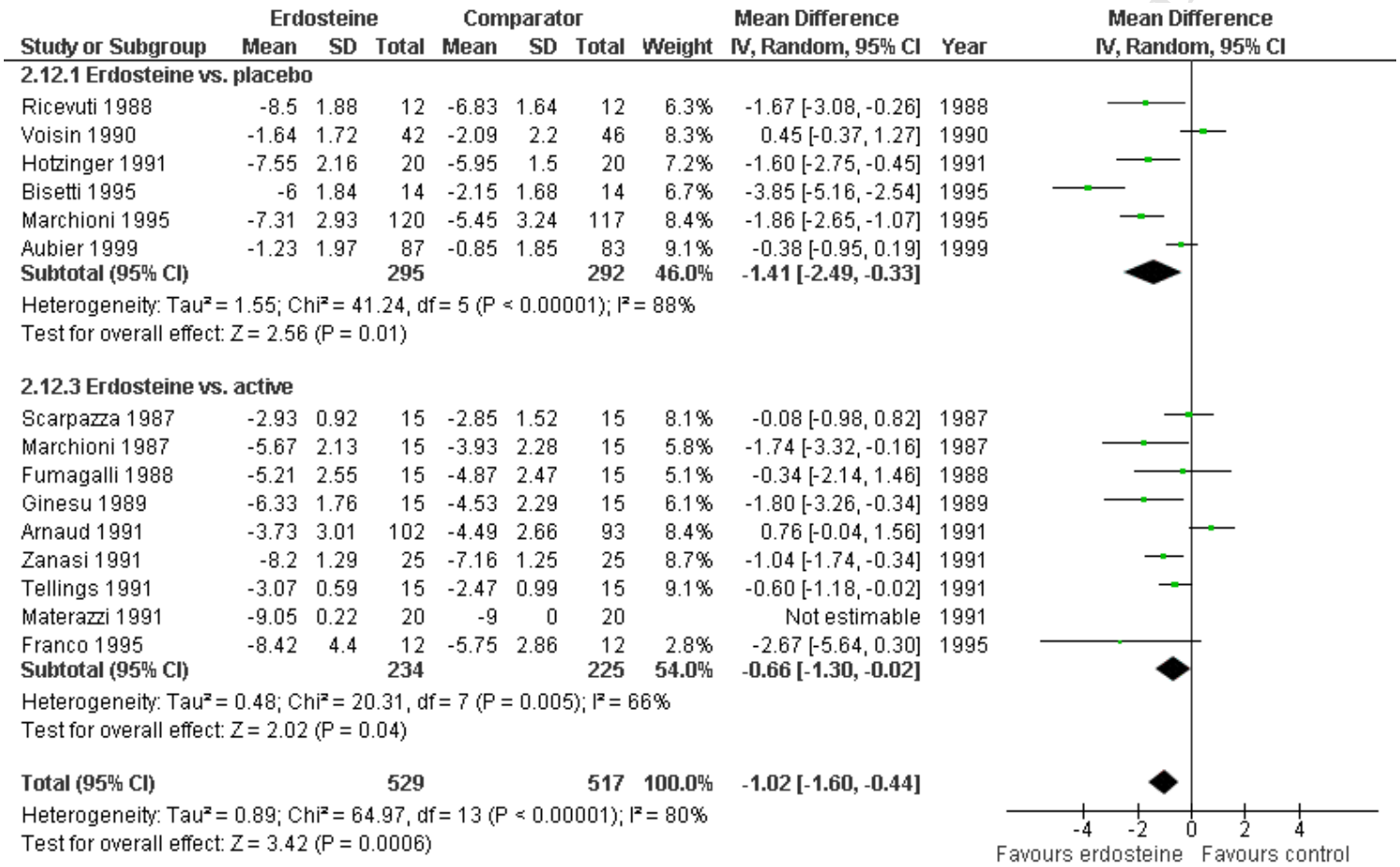

Erdosteine
Comparator
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
2.12.1 Erdosteine vs. placebo
Ricevuti 1988 -8.5 1.88 12 -6.83 1.64 12 6.3% -1.67 [-3.08, -0.26] 1988
Voisin 1990 -1.64 1.72 42 -2.09 2.2 46 8.3% 0.45 [-0.37, 1.27] 1990
Hotzinger 1991 -7.55 2.16 20 -5.95 1.5 20 7.2% -1.60 [-2.75, -0.45] 1991
Bisetti 1995 -6 1.84 14 -2.15 1.68 14 6.7% -3.85 [-5.16, -2.54] 1995
Marchioni 1995 -7.31 2.93 120 -5.45 3.24 117 8.4% -1.86 [-2.65, -1.07] 1995
Aubier 1999 -1.23 1.97 87 -0.85 1.85 83 9.1% -0.38 [-0.95, 0.19] 1999
Subtotal (95% CI) 295 292 46.0% -1.41 [-2.49, -0.33]
Heterogeneity: Tau² = 1.55; Chi² = 41.24, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.56 (P = 0.01)
2.12.3 Erdosteine vs. active
Scarpazza 1987 -2.93 0.92 15 -2.85 1.52 15 8.1% -0.08 [-0.98, 0.82] 1987
Marchioni 1987 -5.67 2.13 15 -3.93 2.28 15 5.8% -1.74 [-3.32, -0.16] 1987
Fumagalli 1988 -5.21 2.55 15 -4.87 2.47 15 5.1% -0.34 [-2.14, 1.46] 1988
Ginesu 1989 -6.33 1.76 15 -4.53 2.29 15 6.1% -1.80 [-3.26, -0.34] 1989
Arnaud 1991 -3.73 3.01 102 -4.49 2.66 93 8.4% 0.76 [-0.04, 1.56] 1991
Zanasi 1991 -8.2 1.29 25 -7.16 1.25 25 8.7% -1.04 [-1.74, -0.34] 1991
Tellings 1991 -3.07 0.59 15 -2.47 0.99 15 9.1% -0.60 [-1.18, -0.02] 1991
Materazzi 1991 -9.05 0.22 20 -9 0 20 Not estimable 1991
Franco 1995 -8.42 4.4 12 -5.75 2.86 12 2.8% -2.67 [-5.64, 0.30] 1995
Subtotal (95% CI) 234 225 54.0% -0.66 [-1.30, -0.02]
Heterogeneity: Tau² = 0.48; Chi² = 20.31, df = 7 (P = 0.005); I² = 66%
Test for overall effect: Z = 2.02 (P = 0.04)
Total (95% CI) 529 517 100.0% -1.02 [-1.60, -0.44]
Heterogeneity: Tau² = 0.89; Chi² = 64.97, df = 13 (P < 0.00001); I² = 80%
Test for overall effect: Z = 3.42 (P = 0.0006)
-4 -2 0 2 4
Favours erdosteine Favours control

**Figure 3**

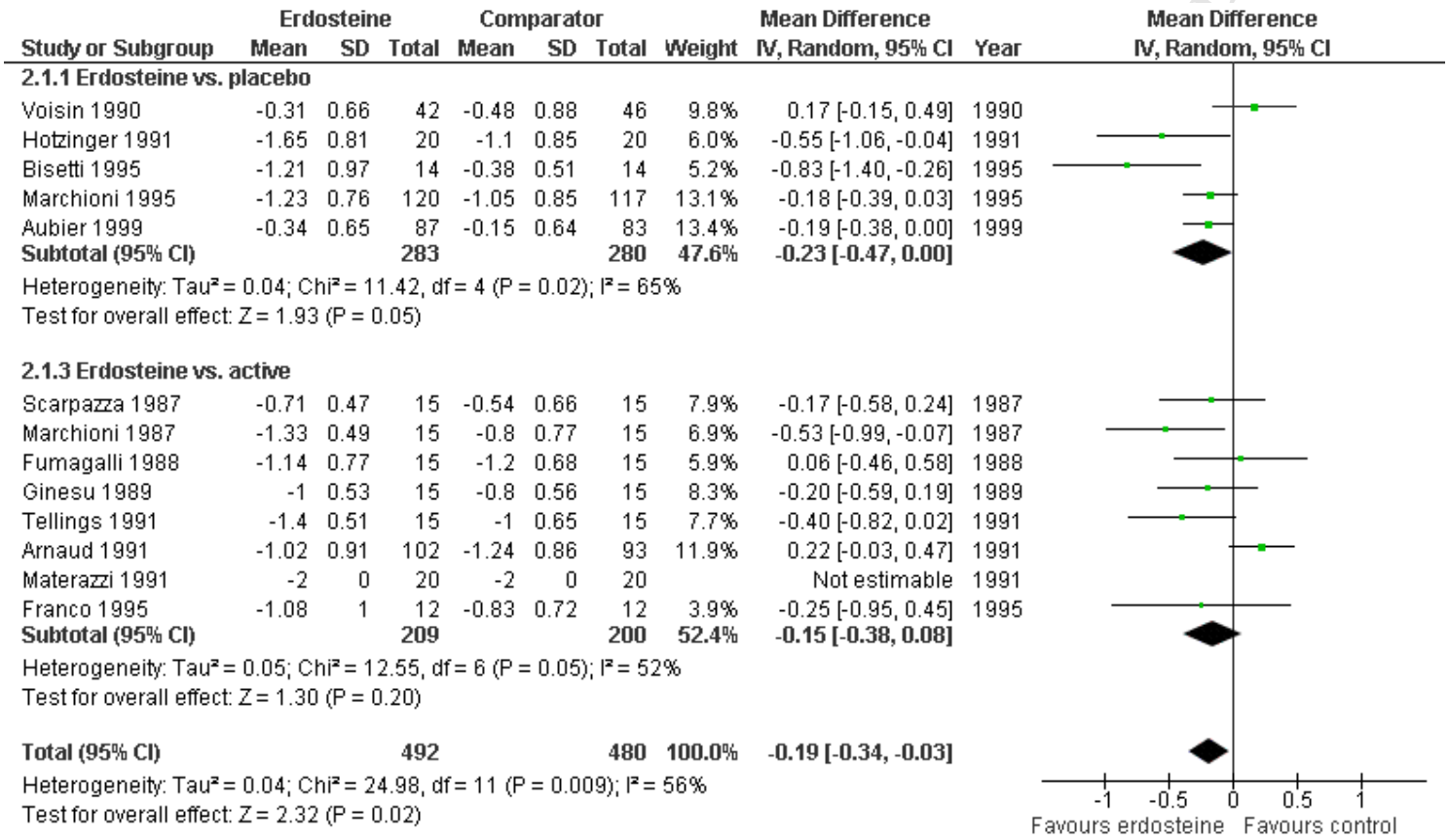

Erdosteine
Comparator
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
2.1.1 Erdosteine vs. placebo
Voisin 1990 -0.31 0.66 42 -0.48 0.88 46 9.8% 0.17 [-0.15, 0.49] 1990
Hotzinger 1991 -1.65 0.81 20 -1.1 0.85 20 6.0% -0.55 [-1.06, -0.04] 1991
Bisetti 1995 -1.21 0.97 14 -0.38 0.51 14 5.2% -0.83 [-1.40, -0.26] 1995
Marchioni 1995 -1.23 0.76 120 -1.05 0.85 117 13.1% -0.18 [-0.39, 0.03] 1995
Aubier 1999 -0.34 0.65 87 -0.15 0.64 83 13.4% -0.19 [-0.38, 0.00] 1999
Subtotal (95% CI) 283 280 47.6% -0.23 [-0.47, 0.00]
Heterogeneity: Tau² = 0.04; Chi² = 11.42, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 1.93 (P = 0.05)
2.1.3 Erdosteine vs. active
Scarpazza 1987 -0.71 0.47 15 -0.54 0.66 15 7.9% -0.17 [-0.58, 0.24] 1987
Marchioni 1987 -1.33 0.49 15 -0.8 0.77 15 6.9% -0.53 [-0.99, -0.07] 1987
Fumagalli 1988 -1.14 0.77 15 -1.2 0.68 15 5.9% 0.06 [-0.46, 0.58] 1988
Ginesu 1989 -1 0.53 15 -0.8 0.56 15 8.3% -0.20 [-0.59, 0.19] 1989
Tellings 1991 -1.4 0.51 15 -1 0.65 15 7.7% -0.40 [-0.82, 0.02] 1991
Arnaud 1991 -1.02 0.91 102 -1.24 0.86 93 11.9% 0.22 [-0.03, 0.47] 1991
Materazzi 1991 -2 0 20 -2 0 20 Not estimable 1991
Franco 1995 -1.08 1 12 -0.83 0.72 12 3.9% -0.25 [-0.95, 0.45] 1995
Subtotal (95% CI) 209 200 52.4% -0.15 [-0.38, 0.08]
Heterogeneity: Tau² = 0.05; Chi² = 12.55, df = 6 (P = 0.05); I² = 52%
Test for overall effect: Z = 1.30 (P = 0.20)
Total (95% CI) 492 480 100.0% -0.19 [-0.34, -0.03]
Heterogeneity: Tau² = 0.04; Chi² = 24.98, df = 11 (P = 0.009); I² = 56%
Test for overall effect: Z = 2.32 (P = 0.02)
-1 -0.5 0 0.5 1
Favours erdosteine Favours control

**Figure 4**

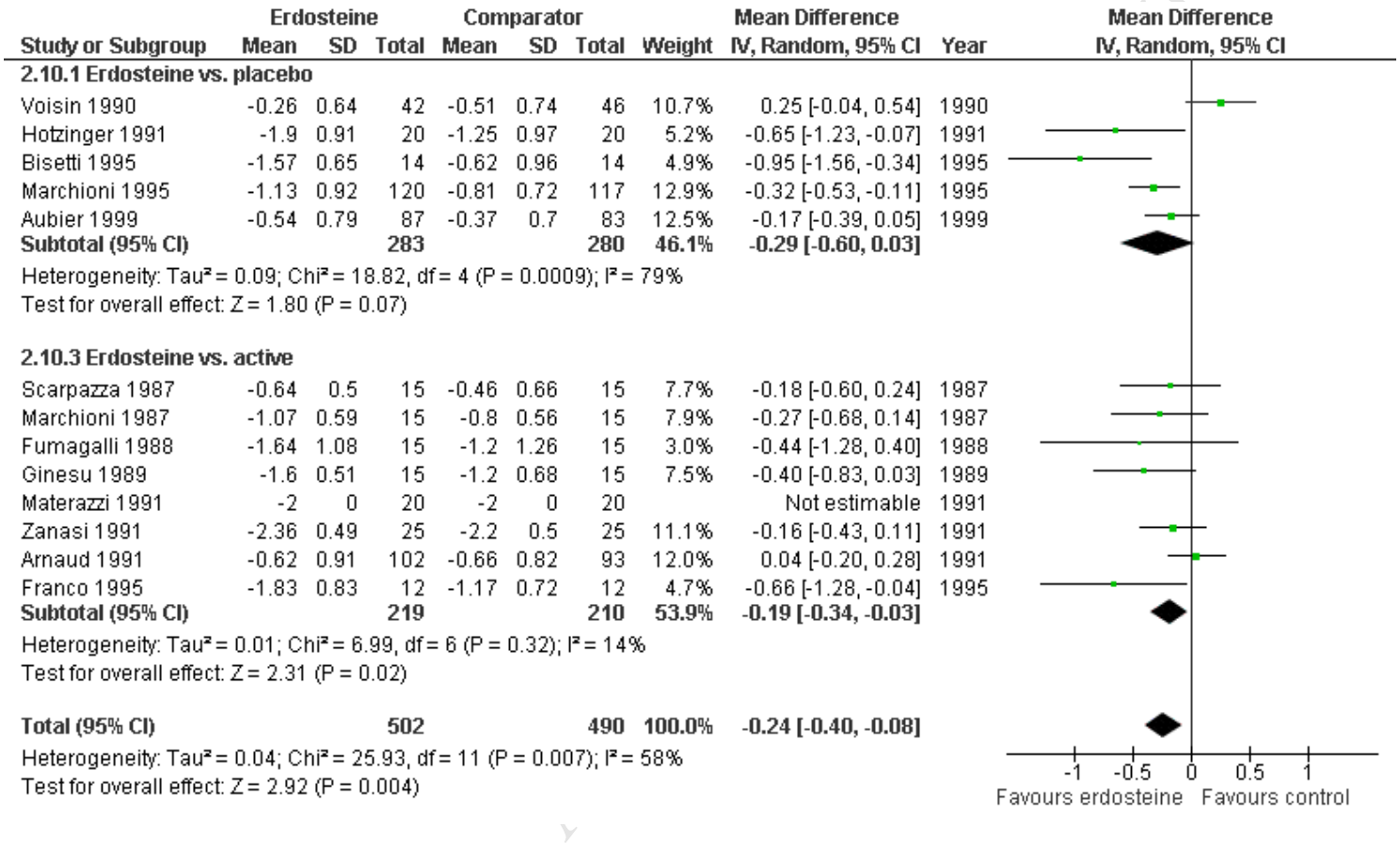
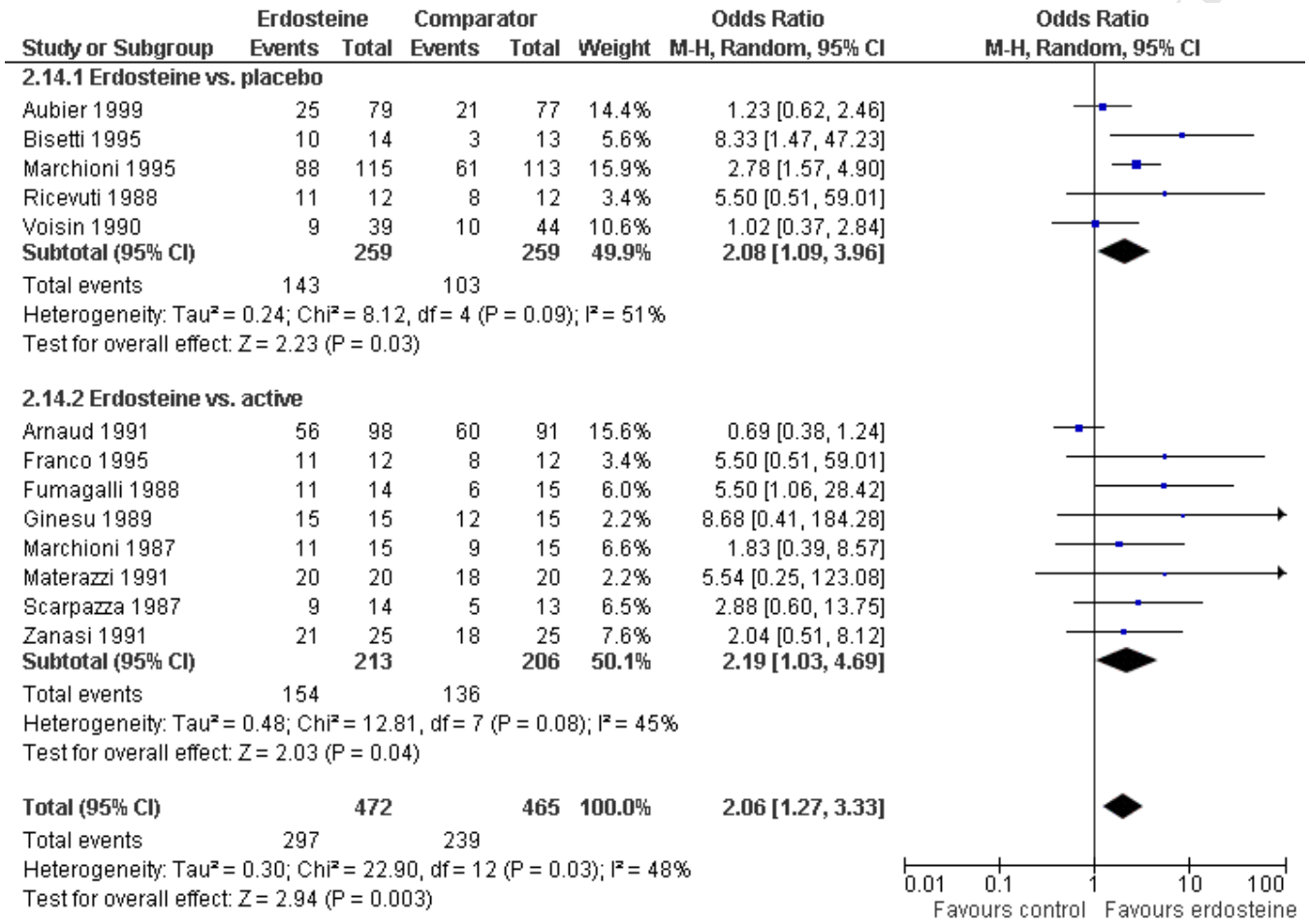

Erdosteine
Comparator
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
2.10.1 Erdosteine vs. placebo
Voisin 1990 -0.26 0.64 42 -0.51 0.74 46 10.7% 0.25 [-0.04, 0.54] 1990
Hotzinger 1991 -1.9 0.91 20 -1.25 0.97 20 5.2% -0.65 [-1.23, -0.07] 1991
Bisetti 1995 -1.57 0.65 14 -0.62 0.96 14 4.9% -0.95 [-1.56, -0.34] 1995
Marchioni 1995 -1.13 0.92 120 -0.81 0.72 117 12.9% -0.32 [-0.53, -0.11] 1995
Aubier 1999 -0.54 0.79 87 -0.37 0.7 83 12.5% -0.17 [-0.39, 0.05] 1999
Subtotal (95% CI) 283 280 46.1% -0.29 [-0.60, 0.03]
Heterogeneity: Tau² = 0.09; Chi² = 18.82, df = 4 (P = 0.0009); I² = 79%
Test for overall effect: Z = 1.80 (P = 0.07)
2.10.3 Erdosteine vs. active
Scarpazza 1987 -0.64 0.5 15 -0.46 0.66 15 7.7% -0.18 [-0.60, 0.24] 1987
Marchioni 1987 -1.07 0.59 15 -0.8 0.56 15 7.9% -0.27 [-0.68, 0.14] 1987
Fumagalli 1988 -1.64 1.08 15 -1.2 1.26 15 3.0% -0.44 [-1.28, 0.40] 1988
Ginesu 1989 -1.6 0.51 15 -1.2 0.68 15 7.5% -0.40 [-0.83, 0.03] 1989
Materazzi 1991 -2 0 20 -2 0 20 Not estimable 1991
Zanasi 1991 -2.36 0.49 25 -2.2 0.5 25 11.1% -0.16 [-0.43, 0.11] 1991
Arnaud 1991 -0.62 0.91 102 -0.66 0.82 93 12.0% 0.04 [-0.20, 0.28] 1991
Franco 1995 -1.83 0.83 12 -1.17 0.72 12 4.7% -0.66 [-1.28, -0.04] 1995
Subtotal (95% CI) 219 210 53.9% -0.19 [-0.34, -0.03]
Heterogeneity: Tau² = 0.01; Chi² = 6.99, df = 6 (P = 0.32); I² = 14%
Test for overall effect: Z = 2.31 (P = 0.02)
Total (95% CI) 502 490 100.0% -0.24 [-0.40, -0.08]
Heterogeneity: Tau² = 0.04; Chi² = 25.93, df = 11 (P = 0.007); I² = 58%
Test for overall effect: Z = 2.92 (P = 0.004)
-1 -0.5 0 0.5 1
Favours erdosteine Favours control

**Figure 5**


Erdosteine
Comparator
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.14.1 Erdosteine vs. placebo
Aubier 1999 25 79 21 77 14.4% 1.23 [0.62, 2.46]
Bisetti 1995 10 14 3 13 5.6% 8.33 [1.47, 47.23]
Marchioni 1995 88 115 61 113 15.9% 2.78 [1.57, 4.90]
Ricevuti 1988 11 12 8 12 3.4% 5.50 [0.51, 59.01]
Voisin 1990 9 39 10 44 10.6% 1.02 [0.37, 2.84]
Subtotal (95% CI) 259 259 49.9% 2.08 [1.09, 3.96]
Total events 143 103
Heterogeneity: Tau² = 0.24; Chi² = 8.12, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 2.23 (P = 0.03)
2.14.2 Erdosteine vs. active
Arnaud 1991 56 98 60 91 15.6% 0.69 [0.38, 1.24]
Franco 1995 11 12 8 12 3.4% 5.50 [0.51, 59.01]
Fumagalli 1988 11 14 6 15 6.0% 5.50 [1.06, 28.42]
Ginesu 1989 15 15 12 15 2.2% 8.68 [0.41, 184.28]
Marchioni 1987 11 15 9 15 6.6% 1.83 [0.39, 8.57]
Materazzi 1991 20 20 18 20 2.2% 5.54 [0.25, 123.08]
Scarpazza 1987 9 14 5 13 6.5% 2.88 [0.60, 13.75]
Zanasi 1991 21 25 18 25 7.6% 2.04 [0.51, 8.12]
Subtotal (95% CI) 213 206 50.1% 2.19 [1.03, 4.69]
Total events 154 136
Heterogeneity: Tau² = 0.48; Chi² = 12.81, df = 7 (P = 0.08); I² = 45%
Test for overall effect: Z = 2.03 (P = 0.04)
Total (95% CI) 472 465 100.0% 2.06 [1.27, 3.33]
Total events 297 239
Heterogeneity: Tau² = 0.30; Chi² = 22.90, df = 12 (P = 0.03); I² = 48%
Test for overall effect: Z = 2.94 (P = 0.003)
0.01 0.1 1 10 100
Favours control Favours erdosteine

## Table 1
## Main characteristics of RCTs included in the meta-analysis

| Ref. | Study design | Patient N | | Study Population | | | Schedule Erdosteine | Schedule Comparator |
|---|---|---|---|---|---|---|---|---|
| | | Randomised /Analysed | Dropouts (E / C) | Median Age, yr./ Proportion Male, % | Diagnosis at inclusion | Concomitant medication | | |
| **Erdosteine *versus* placebo** | | | | | | | | |
| Ricevuti[14] | DB, CT | 24 / 24 | 0 / 0 | 57.0 / 42 | Acute infective exacerbation of chronic bronchitis (amoxicillin-sensitive bacteria isolated from sputum) | Amoxicillin 500 mg tid | 300 mg TID | Placebo^ |
| Voisin[40] | MC, DB, RCT | 88 / 82 | 4 / 2 | 57.5 / 74 | Stable chronic obstructive bronchitis ($FEV_1$/FVC at least 10% below normal theoretical value) | Not available | 300 mg BID | Placebo^ |
| Hotzinger[15] | DB, RCT | 40 / 40 | 0 / 0 | 49.0 / 75 | Hypersecretory infective bronchitis (acute bronchitis or relapses of chronic bronchitis) | Co-trimoxazole 160+800 mg bid | 300 mg TID | Placebo^ |
| Bisetti[39] | DB, RCT | 28 / 27 | 0 / 1 | 62.0 / 68 | Acute exacerbation of chronic bronchitis | Antibiotics Xanthines, $beta_2$-agonists | 300 mg BID | Placebo^ |
| Marchioni[11] | MC, DB, RCT | 237 / 226 | 6 / 5 | 66.0 / 76 | Acute exacerbation of chronic obstructive bronchitis (amoxicillin-sensitive bacteria isolated from sputum; $FEV_1$/FVC at least 10% below normal theoretical value) | Amoxicillin 500 mg tid Xanthines, $beta_2$-agonists | 300 mg BID | Placebo^ |
| Aubier[12] | MC, DB, RCT | 170 / 166 | 1 / 3 | 59.0 / 58 | Stable chronic obstructive bronchitis ($FEV_1$/FVC at least 10% below normal theoretical value) | Xanthines, $beta_2$-agonists | 300 mg BID | Placebo^ |
| **Erdosteine *versus* mucolytics** | | | | | | | | |
| Marchioni[43] | DB, RCT | 30 / 30 | 0 / 0 | 64.5 / 93 | Acute exacerbation of chronic bronchitis | Antibiotics Xanthines, $beta_2$-agonists, steroids | 300 mg BID | Sobrerol 200 mg BID |
| Scarpazza[44] | DB, RCT | 30 / 27 | 1 / 2 | 64.0 / 43 | Acute exacerbation of chronic bronchitis | Antibiotics Xanthines, $beta_2$-agonists | 150 mg TID | Sobrerol 100 mg TID |
| Fumagalli[45] | DB, RCT | 30 / 30 | 0 / 0 | 65.0 / 53 | Acute or chronic exacerbated bronchitis | Antibiotics Xanthines, $beta_2$-agonists, steroids | 300 mg BID | Ambroxol 30 mg BID |
| Ginesu[16] | SB, CT | 30 / 30 | 0 / 0 | 62.5 / 100 | Bronchopulmonary diseases characterised by expectoration and cough | Antibiotics Xanthines, $beta_2$-agonists | 150 mg TID | Ambroxol 30 mg TID |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Tellings[38] | SB, RCT | 30 / 30 | 0 / 0 | 67.0 / 100 | Acute exacerbation of chronic bronchitis | Bacampicillin 800 mg bid | 300 mg BID | Ambroxol 30 mg TID |
| Materazzi[46] | DB, RCT | 40 / 40 | 0 / 0 | 66.0 / 50 | Acute exacerbation of chronic bronchitis | Amoxicillin 1000 mg bid Xanthines | 300 mg BID | N-Acetylcysteine 300 mg BID |
| Zanasi[17] | DB, RCT | 50 / 50 | 0 / 0 | 58.0 / 62 | Acute exacerbation of chronic bronchitis | Parenteral antibiotics | 225 mg TID | N-Acetylcysteine 200 mg TID |
| Franco[18] | SB, RCT | 24 / 24 | 0 / 0 | 66.5 / 83 | Chronic bronchitis requiring mucus-fluidifying treatment | Antibiotics Xanthines, beta$_2$-agonists, steroids | 300 mg TID | Carbocysteine 750 mg TID |
| Arnaud[13] | MC, DB, RCT | 195 / 187 | 5 / 3 | 61.0 / 73 | Acute exacerbation of chronic obstructive bronchitis requiring antibiotic treatment ($FEV_1$/FVC at least 10% below normal theoretical value) | Antibiotics Xanthines, beta$_2$-agonists, steroids | 300 mg TID | N-Acetylcysteine 200 mg TID |

MC = Multicenter; DB = double-blind; SB = single-blind; RCT = randomised controlled trial; CT = Controlled trial; E / C = Erdosteine / Comparators

^ In all cases, placebo capsules are administered with same frequency and duration

**Table 2**
**Study quality assessment according to Jadad scale**

| First Author | Treatment allocation | Double-blind | Description of withdrawals/dropouts | Score |
|---|---|---|---|---|
| ***Published Studies*** | | | | |
| Ricevuti (Thorax 1988)[14] | According to matched demographics | Adequate (placebo) | No withdrawals/dropouts | 2 |
| Hotzinger (Med Praxis 1991)[15] | Random list | Adequate (placebo) | No withdrawals/dropouts | 4 |
| Bisetti (Arch Med Int 1995)[39] | Random list | Adequate (placebo) | Adequate | 5 |
| Marchioni (Int J Clin Pharm Ther 1995)[11] | Random list | Adequate (placebo) | Adequate | 5 |
| Aubier (Rev Mal Respir 1999)[12] | Random list | Adequate (placebo) | Adequate | 5 |
| Fumagalli (It J Chest Dis 1988)[45] | Random list | Blinding method not described | Adequate | 3 |
| Tellings (Med Praxis 1991)[38] | Random list | No (single-blind) | No withdrawals/dropouts | 2 |
| Zanasi (Med Praxis 1991)[17] | Random list | Adequate (identical sachets) | No withdrawals/dropouts | 4 |
| Franco (Arch Med Int 1995)[18] | Random list | No (single-blind) | No withdrawals/dropouts | 2 |
| ***Unpublished Studies*** | | | | |
| *Voisin (CSR 1990)[40]* | *Random list* | *Adequate (placebo)* | *Adequate* | *5* |
| *Marchioni (CSR 1987)[43]* | *Random list* | *Blinding method not described* | *No withdrawals/dropouts* | *2* |
| *Scarpazza (CSR 1987)[44]* | *Random list* | *Blinding method not described* | *Adequate* | *3* |
| *Ginesu (CSR 1989)[16]* | *Alternatively* | *No (single-blind)* | *No withdrawals/dropouts* | *1* |
| *Materazzi (CSR 1991)[46]* | *Inadequate random list* | *Adequate (identical cps.)* | *No withdrawals/dropouts* | *2* |
| *Arnaud (CSR 1991)[13]* | *Random list* | *Adequate (double-dummy)* | *Adequate* | *5* |

CSR = Clinical Study Report

## Table 3
## Patient Characteristics

| | Erdosteine | Comparator |
|---|---|---|
| **Erdosteine *versus* Placebo** | **N = 295** | **N = 292** |
| ***Age (yrs.)*[§]** | 59.6 (11.9) | 59.9 (12.4) |
| ***Sex M/F*** | 198 / 97 | 205 / 87 |
| ***Diagnosis N (%)*** | | |
| Exacerbations of CB/COPD | 156 (52.9%) | 153 (52.4%) |
| Stable obstructive bronchitis | 129 (43.7%) | 129 (44.2%) |
| Acute bronchitis/Pneumonia | 7 (2.4%) | 7 (2.4%) |
| Others | 3 (1.0%) | 3 (1.0%) |
| ***Concomitant medication R03 N (%)^*** | *n = 253* | *n = 246* |
| Antibiotics | 163 (64.4%) | 160 (65.0%) |
| Bronchodilators (beta$_2$-agonists/ xanthines) | 76 (30.0%) | 77 (31.3%) |
| ***Pulmonary function*[§]** | *n = 237* | *n = 236* |
| $FEV_1$ (L) | 1.55 (0.74) | 1.56 (0.76) |
| $FEV_1$ (% pred.) | 55.7% (22.4) | 55.5% (22.6) |
| $FEV_1$ / FVC (%) | 58.2% (13.4) | 58.6% (15.5) |
| **Erdosteine *versus* Mucolytics** | **N = 234** | **N = 225** |
| ***Age (yrs.)*[§]** | 61.7 (10.8) | 61.5 (11.6) |
| ***Sex (M/F)*** | 173 / 61 | 157 / 68 |
| ***Diagnosis N (%)*** | | |
| Exacerbations of CB/COPD | 220 (94.0%) | 211 (93.8%) |
| Stable obstructive bronchitis | 9 (3.8%) | 8 (3.6%) |
| Acute bronchitis/Pneumonia | 3 (1.3%) | 2 (0.9%) |
| Others | 2 (0.9%) | 4 (1.8%) |
| ***Concomitant medication R03 N (%)^*** | *n = 209* | *n = 200* |
| Antibiotics | 187 (89.5%) | 182 (91.0%) |
| Bronchodilators (beta$_2$-agonists/ xanthines) | 88 (42.1%) | 91 (45.5%) |
| Steroids | 12 (5.7%) | 15 (7.5%) |
| ***Pulmonary function*[§]** | *n = 141* | *n = 138* |
| $FEV_1$ (L) | 1.42 (0.54) | 1.42 (0.55) |
| $FEV_1$ (% pred.) | 55.3% (20.1) | 56.1% (19.0) |
| $FEV_1$ / FVC (%) | 59.4 (13.8) | 61.5 (15.2) |

[§] Data are mean (SD)
^ Data from 1 study vs. placebo and 1 study vs. mucolytics: not available.

**Table 4**
**Outcome data on individual respiratory symptoms from the RCTs included in the meta-analysis**

| Ref. | Cough frequency | Cough intensity | Sputum viscosity | Sputum purulence | Difficulty to expectorate | Catarrh ronchi at auscultation | Dyspnoea |
|---|---|---|---|---|---|---|---|
| **Erdosteine *versus* placebo** | | | | | | | |
| Ricevuti[14] | NA | -0.33 [-0.85, 0.19] | -0.58 [-1.03, -0.13] | -0.34 [-0.65, -0.03] | NA | NA | -0.42 [-1.03, 0.19] |
| Voisin[40] | 0.17 [-0.15, 0.49] | NA | 0.07 [-0.20, 0.34] | 0.19 [-0.07, 0.45] | 0.25 [-0.04, 0.54] | NA | -0.12 [-0.44, 0.20] |
| Hotzinger[15] | -0.55 [-1.06, -0.04] | -0.40 [-0.81, 0.01] | NA | 0.00 [-0.35, 0.35] | -0.65 [-1.23, -0.07] | NA | NA |
| Bisetti[39] | -0.83 [-1.40, -0.26] | -0.89 [-1.33, -0.45] | NA | -0.33 [-0.88, 0.22] | -0.95 [-1.56, -0.34] | -0.83 [-1.14, -0.52] | NA |
| Marchioni[11] | -0.18 [-0.39, 0.03] | NA | -0.41 [-0.60, -0.22] | -0.43 [-0.61, -0.25] | -0.32 [-0.53, -0.11] | -0.41 [-0.62, -0.20] | -0.21 [-0.41, -0.01] |
| Aubier[12] | -0.19 [-0.38, 0.00] | -0.14 [-0.37, 0.09] | -0.24 [-0.46, -0.02] | NA | -0.17 [-0.39, 0.05] | NA | -0.14 [-0.32, 0.04] |
| *Subtotal* | *-0.23 [-0.47, 0.00]* | *-0.42 [-0.75, -0.08]* | *-0.27 [-0.51, -0.03]* | *-0.18 [-0.46, 0.10]* | *-0.29 [-0.60, 0.03]* | *-0.60 [-1.01, -0.19]* | *-0.17 [-0.30, -0.05]* |
| **Erdosteine *versus* Mucolytics** | | | | | | | |
| Marchioni[43] | -0.53 [-0.99, -0.07] | -0.26 [-0.60, 0.08] | NA | -0.27 [-0.83, 0.29] | -0.27 [-0.68, 0.14] | -0.40 [-0.80, -0.00] | NA |
| Scarpazza[44] | -0.17 [-0.58, 0.24] | NA | NA | 0.06 [-0.33, 0.45] | -0.18 [-0.60, 0.24] | 0.22 [-0.09, 0.53] | NA |
| Fumagalli[45] | 0.06 [-0.46, 0.58] | -0.07 [-0.60, 0.46] | NA | 0.11 [-0.50, 0.72] | -0.44 [-1.28, 0.40] | NA | NA |
| Ginesu[16] | -0.20 [-0.59, 0.19] | -0.27 [-0.64, 0.10] | -0.54 [-0.98, -0.10] | NA | -0.40 [-0.83, 0.03] | -0.34 [-0.69, 0.01] | -0.06 [-0.45, 0.33] |
| Tellings[38] | -0.40 [-0.82, 0.02] | -0.20 [-0.56, 0.16] | NA | NA | NA | NA | NA |
| Materazzi[46] | NE | NE | NE | NA | NE | NE | NA |
| Zanasi[17] | NA | -0.44 [-0.83, -0.05] | NA | -0.20 [-0.55, 0.15] | -0.16 [-0.43, 0.11] | -0.24 [-0.56, 0.08] | NA |
| Franco[18] | -0.25 [-0.95, 0.45] | -0.25 [-0.90, 0.40] | -0.75 [-1.40, -0.10] | -0.25 [-0.89, 0.39] | -0.66 [-1.28, -0.04] | -0.50 [-1.13, 0.13] | NA |
| Arnaud[13] | 0.22 [-0.03, 0.47] | NA | 0.06 [-0.21, 0.33] | 0.20 [-0.04, 0.44] | 0.04 [-0.20, 0.28] | NA | 0.23 [-0.01, 0.47] |
| *Subtotal* | *-0.15 [-0.38, 0.08]* | *-0.26 [-0.43, -0.10]* | *-0.36 [-0.87, 0.16]* | *0.02 [-0.15, 0.19]* | *-0.19 [-0.34, -0.03]* | *-0.21 [-0.48, 0.05]* | *0.13 [-0.14, 0.40]* |
| **Total** | **-0.19 [-0.34, -0.03] P = 0.02** | **-0.30 [-0.44, -0.17] P < 0.00001** | **-0.28 [-0.49, -0.07] P = 0.008** | **-0.11 [-0.28, 0.07] P = 0.25** | **-0.24 [-0.40, -0.08] P = 0.004** | **-0.35 [-0.60, -0.10] P = 0.006** | **-0.09 [-0.24, 0.07] P = 0.29** |

Between-treatment Mean Difference [95%CI]

NE = not estimable; NA = not available

**Table 5**
**Incidence of Adverse Events**

| | Erdosteine | Reference |
|---|---|---|
| **Erdosteine *versus* Placebo** | **N = 295** | **N = 292** |
| ***No. Patients reporting AEs N (%)*** | | |
| ***Gastrointestinal*** | 21 | 24 |
| ***Taste Loss*** | 1 | 0 |
| ***Allergic reactions*** | 2 | 3 |
| ***Miscellaneous*** | 11 | 5 |
| ***Total*** | 35 (11.9%) | 32 (11.0%) |
| **Erdosteine *versus* Mucolytics** | **N = 234** | **N = 225** |
| ***No. Patients reporting AEs N (%)*** | | |
| ***Gastrointestinal*** | 11 | 19 |
| ***Taste Loss*** | 0 | 0 |
| ***Allergic reactions*** | 1 | 0 |
| ***Miscellaneous*** | 7 | 6 |
| ***Total*** | 19 (8.1%) | 25 (11.1%) |