CLINICAL TRIAL REPORT SYNOPSIS

Study 7171L01

Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
Zambon S.p.A.		
Name of finished product **Fluimucil®**		
Name of active ingredient **N-acetylcysteine**		

Title of the study

A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL GROUPS STUDY ON EFFICACY AND SAFETY OF NAC 600 MG DAILY AND NAC 1200 MG DAILY AS MUCOLYTIC AGENT IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) EXACERBATION.

Principal Investigators and study sites

The study took place in Italy and involved 78 recruiters General Practitioners, in 5 ASL (Foligno, Imperia, Genova, Massa, Perugia).

001: Buccelli (S. Lorenzo al mare, IM); 002: Pinelli (Imperia, IM); 003: Amoretti (Imperia, IM); 005: Lanteri (Imperia, IM); 006: Novaro (Imperia, IM); 007: Dolmetta (Imperia, IM); 011: Baglioni (Torgiano, PG); 013: Bensi (Assisi, PG); 014: Berardi (Perugia, PG); 017: Coppini (Perugia, PG); 018: Draghini (Torgiano, PG); 019: Germini (Perugia, PG); 022: Lindi (Ponte Pattoli, PG); 023: Mezzetti (Perugia, PG); 024: Natali (Perugia, PG); 027: Pannacci (Ponte S. Giovanni, PG); 028: Parretti (Perugia, PG); 030: Rossi (Perugia, PG); 031: Scarponi (Perugia, PG); 034: Tedeschi (Perugia, PG); 035: Urbani (Perugia, PG); 042: Cecchini (Foligno, PG); 043: De Motoli (Spoleto, PG); 046: Gentili (Borgo Trevi, PG); 048: Marcucci (Spoleto, PG); 050: Pieroni (Spoleto, PG); 051: Piselli (Spoleto, PG); 053: Simoneschi (Spoleto, PG); 054: Sperandio (Foligno, PG); 056: Surano (Montefalco, PG); 057: Trampetti (Spoleto, PG); 061: Acquarone (Genova, GE); 062: Brasesco (Genova, GE); 066: Di Benedetto (Genova, GE); 068: Fonzi (Genova, GE); 069: Gaggino (Genova, GE); 071: Ghini (Genova, GE); 072: Guida (Cogoleto, GE); 074: Lavagnino (S. Olcese, GE); 075: Malatesta (Cogoleto, GE); 076: Masserano (S. Olcese, GE); 077: Montarsolo (Cogoleto, GE); 078: Pesce (Cogoleto, GE); 079: Picciotto (Arenzano, GE); 080: Primi (Genova, GE); 081: Roccatagliata (Genova, GE); 083: Saccarello (Masone, GE); 084: Stellini (Genova, GE); 086: Storace (Ronco Scrivia, GE); 087: Valente (Genova, GE); 088: Vallarino (Arenzano, GE); 150: Amato (Genova, GE); 152: Bochicchio (Genova, GE); 154: Castrogiovanni (Genova, GE); 159: Mari (Genova, GE); 160: Massardo (Genova, GE); 163: Ottonello (Genova, GE); 164: Percivale (Busalla, GE); 165: Messina (Genova, GE); 166: Pesenti (Genova, GE); 167: Proietti (Genova, GE); 169: Robino (Rossiglione, GE); 170: Tamagno (Savignone, GE); 121: Agati (Sanremo, IM); 124: Barletta (Vallecrosia, IM); 125: Berlingiero (Ventimiglia, IM); 126: Bessone (Imperia, IM); 132: Gatani (Imperia, IM); 133: Graffigna (Sanremo, IM); 136: Minaglia (Sanremo, IM); 137: Mondino (Bordighera, IM); 140: Senio (Ventimiglia, IM); 141: Tamborra (Bordighera, IM); 101: Cesaretti (Marina di Massa, MS); 103: Galli (Licciana Nardi, MS); 104: Mannari (Massa, MS); 106: Panvini (Fivizzano, MS); 107: Porcelli (Gassano, MS).

Publication (reference)	*Clinical phase*
none	Phase III
Date of first enrolment	***Date of last completed***
29 January 2007 (1st patient randomized)	30 June 2008 (last patient, last visit)

Objectives

Primary Objective

To show that both treatments with NAC 600 mg/day and NAC 1,200 mg/day exhibit a superior efficacy, in terms of reduction of the BCSS composite score (Breathlessness, Cough and Sputum Scale) versus placebo in patients with COPD exacerbation.

Secondary Objectives

1. To evaluate a dose escalation effect for doses of 600 and 1,200 mg/day of NAC in reducing composite score in patients with COPD exacerbation

In the treatment groups:

2. To compare the time for remission of symptoms and the number of recovered patients.
3. To compare the number of sleep awakenings due to cough.
4. To compare the consumptions of medications prescribed for COPD exacerbation.
5. To compare the number of patients with hospitalizations for COPD.
6. To compare the change from baseline of FEV_1 and FEV_6.
7. To compare the change from baseline of the patient's well-being.
8. To evaluate the safety of the treatment with NAC 600 mg/day and NAC 1,200 mg/day in terms of incidence of adverse events.
9. To evaluate the global efficacy and tolerability of the treatment with NAC 600 mg/day and NAC 1,200 mg/day.

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Name of active ingredient **N-acetylcysteine**		

Study design and methodology

Prospective, double-blind, stratified-randomized, placebo controlled, three-parallel groups, multi-centre, national study. The randomization is stratified according to severity of COPD (stage II and III) for balance between treatment groups. The study involved 78 Italian GPs located in five Italian Local Health Authorities (ASLs), and enrolment was competitive among sites. Each site could enrol a maximum of 36 patients.

Patients were screened and enrolled in the study in the same day upon exacerbation diagnosis as per inclusion criteria and started treatment administration the day after, in the morning for 10 days. They were visited on day 5 and on day 10, at the end of treatment. A follow-up visit or phone call was also foreseen about 30 days after study enter. .

Prior to inclusion, systemic or inhaled antibiotics, oral or parenteral corticosteroids, expectorants, mucolytics, cough suppressant and antioxidants were not admitted, and if the patient was taking any of these, the patient was not to be enrolled.

During the study, expectorants, other mucolytics, antioxidants and cough suppressant were not allowed. The consumption of inhaled bronchodilators and corticosteroids was monitored by the patient recording daily on the diary card the number of puffs. The consumption of the other medications taken to manage the exacerbation of COPD after randomization (systemic or inhaled antibiotics, systemic corticosteroids, anticholinergics, other bronchodilators, theophylline, anti-inflammatory drugs) was monitored by recording start and stop dates of each medication.

Patient population

A total of 750 patients were foreseen in the protocol to have 600 evaluable patients for efficacy analyses. As a result the study was stopped at 714 as low drop-out rate was encountered and almost all patients had completed diary cards up to day 5 (primary endpoint).

Evaluation groups	Placebo n (%)	NAC 600mg n (%)	NAC 1200mg n (%)	All n (%)
Randomised set	247 (100.0%)	238 (100.0%)	229 (100.0%)	714 (100.0%)
Safety set	247 (100.0%)	238 (100.0%)	228 (99.6%)	713 (99.9%)
Full analysis set	241 (97.6%)	233 (97.9%)	225 (98.3%)	699 (97.9%)
Per protocol set	230 (93.1%)	217 (91.2%)	211 (92.1%)	658 (92.2%)

Diagnosis and main criteria for inclusions

Diagnosis. Male or female adult (> 40 years old) patients with a clinical diagnosis of exacerbation of COPD according to Anthonisen's criteria (Anthonisen et al., 1987) were eligible in the study with at least one of this symptoms:

i) increased sputum volume;
ii) increased spututm purulence
iii) increased dyspnoea

In case of only one symptom, at least one of these were also to be present: an upper respiratory tract infection in the previous five days; increased wheezing; increased cough; fever without an obvious source; a 20% increase in respiratory rate or heart rate above baseline.

Inclusion criteria. Patients must meet all the following criteria in order to be eligible for inclusion:

- Written informed consent.
- Outpatients, male or female, aged 40 or over.
- Patients with diagnosis of COPD according to ATS/ERS guidelines (Celli et al, 2004), documented within one year prior to randomization.
- Patients with a clinical diagnosis of exacerbation according to Anthonisen's criteria (Anthonisen et al., 1987) who, at the screening visit, are classified as moderate or severe according to ATS/ERS COPD guidelines

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(Celli et al., 2004):
- Moderate COPD (GOLD stage II): FEV1/FVC <70% and 50≤FEV1<80%
- Severe COPD (GOLD stage III): FEV1/FVC <70% and 30≤FEV1<50%

- Patients with BCSS cumulative score ≥5 at the screening visit.

Exclusion criteria. pregnant or lactating women, or women of childbearing age not using an acceptable method of contraception (surgical sterilization, or practising .an acceptable method of birth control such as oral hormonal contraceptives or Intrauterine Device); patients requiring mechanical airway management; previous (<2weeks) or concomitant treatments with any systemic or inhaled antibiotic, systemic corticosteroids, expectorants, mucolytics, cough suppressants, antioxidants; patients classified, at screening visit: - Mild COPD (GOLD stage I): FEV1/FVC<70% and FEV1 >80%, - Very severe COPD (GOLD stage IV): FEV1/FVC<70% and FEV1 < 30%; hospitalized patients and patients from institutional care facilities; patients with a known diagnosis of bronchial asthma, cystic fibrosis, active pulmonary tuberculosis, pneumonia, bronchial pneumonia, bronchiectasis, lung cancer or lung metastases, other progressively fatal disease, or life expectancy less than three months; Patients with severe cardiovascular diseases such as NYHA class III or IV congestive heart failure or history of stroke, severe neurological or any other disease interfering with study results and the compliance with study protocol; immuno-compromised patients; phenylketonuria due to the presence of aspartame in the study product; patients with suspected or known hypersensitivity to the study product; patients known to have conditions affecting study drug absorption or documented active ulcer within the last three years or severely impaired hepatic or renal function; patients presenting poor reliability (e.g. history of alcohol or drug abuse, bad mental conditions); patients already enrolled in this study or patients who have received any other investigational drug within 1 month prior to study entry, or have such treatment planned for the study period.

Test product, dose and mode of administration, batch number

	N-acetylcysteine (test product)	N-acetylcysteine (test product)	Placebo (comparator)
Dosage	600 mg, (once daily)	1,200 mg, (once daily)	once daily
Duration of the therapy	10 days	10 days	10 days
Mode of administration	Oral (effervescent tablets)	Oral (effervescent tablets)	Oral (effervescent tablets)
Batch number	136-1P249	135-1-1P249	344-1-1P20
Expiry date	October 2008	October 2008	October 2008

The drugs were to be administered once daily, at the same time point in the morning, during the whole treatment period.

Criteria for evaluation

Efficacy

Composite symptom score was reported daily by patient's self assessment using the BCSS, a validated 5 point scale per each symptom (total BCSS calculated as the sum of the 3 single symptom scores) .The baseline value were recorded in the patient's diary the evening before the day of first dose. The score on day 10 is the end of treatment value.

Spirometric assessment. FEV_1 and FEV_6 were measured using PiKo-6 (a device to assess the expiratory flow) in patients by the Investigator at visits 1, 2 and 3 (not mandatory at visits 4). The best 3 readings were selected The values recorded at visit 1 were considered as baseline values.

Number of sleep awaking due to the cough was reported in the patient's diary.

Daily consumption of COPD medication was reported in the patient's diary as a daily number of puff of inhaled medications

Global patient's well-being. Overall judgement of the well being was assessed using a VAS by the patient at visits 1 and 3.

Global efficacy of the treatment was assessed by the Investigator at visit 3 using a 4-point scale.

Clinical outcome. At the follow-up visit, the Investigator had to collect, by phone or during a visit, the patient's clinical outcome of the episode of exacerbation.

Adverse Events were collected from patient's inclusion up to follow-up visit.

Physical examination including vital signs and chest examination were assessed at baseline and at the end of treatment.

The global tolerability was assessed by the Investigator, on a 4-point scale at visit 3.

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Statistical methods

Primary analysis

The primary efficacy endpoint was the change from baseline in the BCSS composite score **at day 5** of treatment (visit 2), by summing up breathlessness, cough and sputum scores. Primary analysis focused on both NAC doses (600 mg/day and 1200mg/day) compared to placebo. The comparison between 600 mg/day and 1200mg/day NAC doses for the change from baseline in the composite score at day 5 of treatment (Visit 2) was considered as a secondary endpoint. A composite score assessment was considered as valid if none of its 3 components was missing. Missing values for any cause were replaced using the Last Observation Carried Forward (LOCF) method, using the last valid composite score assessment available on the diary card after first study medication intake.
The difference between day 5 (or last valid assessment of composite BCSS score available between randomisation and day 5) and baseline scores was computed. The effect of treatment on each of the three single score components (breathlessness, cough and sputum) was additionally explored. Primary analysis was performed using a covariance analysis (ANCOVA) with the baseline composite score as covariate: the model included treatment (placebo, NAC 600 mg/day, NAC 1200 mg/day), GOLD class (stage II, stage III) and centre as fixed effects.

Secondary analyses

The difference between the final assessment (D10 or last not missing assessment) and baseline in BCSS score; the cumulative BCSS score from day 1 to the end of treatment by summing up all scores assessed on the diary and subtracting the baseline value (cumulative score and BCSS sub-score were analysed as previously described for the primary variable); the change from baseline in FEV1, FEV6 and FEV1/FEV6 and FEV1 expressed as % of expected value to mid-treatment and end of treatment; the change from baseline to end of treatment in VAS well-being measurement; the time to recovery defined as a reduction of 50% on the BCSS global score and total number of recovered patients on the basis of the daily patient assessments (D1 to D10); number of sleep awakenings due to cough, assessed at D5 (or the last not missing) assessment on the diary card and at the end of treatment (D10 or last not missing assessment); the daily consumption of medications prescribed for COPD exacerbation from D1 to D10, assessed on the diary card.

A Cox proportional hazard model including smoking habit and GOLD stage as covariate was planned to be used to compare treatment groups for the time to recovery.

The change from baseline in the number of sleep awakenings due to the cough, the number of patients with hospitalization for COPD, the consumption of medications prescribed for COPD exacerbation and the global efficacy according to the investigator, were analysed using non parametric methods.

Safety data

All patients who received at least 1 dose of study medication were included in the safety analyses.

SUMMARY

Efficacy results

BCSS total scores showed on the Full Analysis Set (FAS) versus baseline a highly significant decrease at day 5 of treatment in all treatment groups: -3.0 (-42.3%), -2.6 (-37.1%) and -2.7 (-38.0%) respectively for placebo, NAC 600 and NAC 1,200, but no difference was observed between treatment groups (NAC 600 mg vs placebo p=0.28 and NAC 1200 mg vs placebo p=0.31). No significant difference between treatment groups was observed on single BCSS sub-scores either. As the GOLD category is a significant factor in the primary variable analysis ($p<0.05$ at day 5 and p=0.0005 at day 10) an addition analysis by COPD stage was performed. A greater improvement was shown in the subgroup with moderate GOLD stage, but no treatment effect was observed at any time in any GOLD class. Similar results were observed on the Per Protocol (PP) set.

Results obtained on the cumulative BCSS global score and sub-scores are similar to those of BCSS daily score.

Results on spirometric parameters show that both NAC groups had a better FEV_1 improvement compared to placebo. This improvement (5.3% 4.4% and 3.0% for NAC 600, NAC 1200 and placebo respectively at FAS) is significant on D5 for NAC 600 mg in the FAS analysis (FEV_1 p=0.021; FEV1% p=0.027) and PP analysis (FEV_1 p=0.028; FEV_1% p=0.031), and a trend toward significance was observed for NAC 1200 mg in the PP analysis (FEV_1 D5 p=0.056 and D10 p=0.080). A further improvement was observed in all three groups at the end of treatment: placebo patients exhibited a lower mean score than NAC treated patients. In the NAC 600 mg group a statistically significant improvement also for FEV_6 on D5 was observed (p=0.049).

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For FEV_1/FEV_6 ratio all groups had a highly significant increase from baseline. In the PP set, NAC 1200 had the highest improvement with a trend towards significance in the difference from placebo (D5 p=0.096 and D10 p=0.068), but not different from NAC 600. GOLD stage effect is significant for most parameters/visit when considered separately: patients with moderate COPD showed a better improvement also with placebo; NAC groups showed better results but difference is significant only for NAC 600 vs placebo at D5 (FEV_1 p=0.021 and FEV_1% p=0.027 in FAS; FEV_1 p=0.028 and FEV_1% p=0.031 in PP set).

In severe COPD subgroup, placebo patients did not have any improvement at visit 2, whereas NAC groups continue to significantly improve during treatment: a trend toward significance is obtained for the highest dosage in the PP set (NAC 1200 vs placebo p=0.039 at D5 and p=0.026 at D10). Also inhaled corticosteroids (ICS) as fixed effect was explored. The interaction is positive at D10 for some parameters. So significant differences were found in patients with no concomitant ICS confirming the data on the total population. For patient's Well Being, assessed at the end of the treatment on a VAS, similar results are obtained in the 3 treatment groups even if a slightly better improvement seems to be achieved with NAC in the moderate group as suggested by the nearly significant treatment by GOLD stage interaction (p=0.089 in the FAS). Final Global efficacy assessed by the investigator showed a similar pattern in all treatment groups, even if the number of doubtful results seemed higher in the placebo group. No difference was found between treatment groups in the number of sleep awaking and the daily consumption of COPD medication. Clinical outcome as assessed by the investigator during the follow-up visit: almost all patients were considered by the physician as resolved (≅ 50%) or improved (≅40%); the number of unchanged patients is slightly higher in the placebo group (9%) than in the NAC groups (respectively 3.5% and 6.4% in the 600 mg and 1200 mg groups).

Safety results

Both NAC 600 and NAC 1200 showed a very good safety profile in patients with acute exacerbation of COPD for a 10-day treatment. Safety profile of the two doses of NAC are similar to placebo in the incidence by system organ class, being gastrointestinal disorders the most frequently observed, in severity and all AEs resolved in few days and did not require treatment.

Excluding respiratory symptoms due to the disease under study, the most frequent related AEs were gastrointestinal disorders in all groups.

In addition, also according to the double blind investigator's assessment, the global tolerability of NAC 600 and NAC 1200 was considered substantially similar to placebo.

Conclusions

This study demonstrates that the treatment of acute exacerbation of COPD with NAC 600mg significantly improves, compared to placebo, the airway functionality in terms of spirometric parameters (FEV_1, FEV_6, and FEV_1/FEV_6 ratio) assessed after 5 and 10 days of treatment. However, in spite of the positive results on spirometric parameters, this study did not show differences between groups in diary composite symptoms score, being the placebo responders on symptoms an unexpected very large number. These results are not surprising in the light of the very high variability in COPD exacerbations as reported by other studies. This might suggest that in a once-a-day administration, NAC 600mg is the best effective dose and multiple doses can be more appropriate for a greater benefit as reported in several studies. In conclusion, the new formulation of NAC 1,200 mg apparently does not show a global advantage in a short term once daily administration. This study still confirms the very good safety profile of NAC.

Date of the report

06 September 2010