SYNOPSIS

Name of Sponsor Company	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
Zambon	PART: [.....]	
Name of finished product	VOLUME: [.....]	
Fluimucil		
Name of active ingredient	PAGE: [.....]	
N-acetylcysteine		

Title of the study

AEROSOL TREATMENT OF THE INTERCRITICAL PHASES OF RECURRENT ACUTE RHINOSINUSITIS: A SINGLE BLIND CLINICAL STUDY OF N-ACETYLCYSTEINE VS AMBROXOL ASSOCIATED TO CORTICOSTEROID THERAPY

Principal Investigators and study sites

Prof. PPD ,Italy

Publication (reference)

Unpublished

Study Period:	*Phase of Development*
05/05/2008 (First Subject In) - 26/05/2009 (Last Subject Out)	Phase III

Objectives

Primary Objective: to evaluate the efficacy of the experimental therapy in the resolution of rhinosinusal symptoms deriving from the alteration of ventilatory function and mucociliary transport in rhinosinusal structures, by assessing the proportion of patients who experience a symptomatic improvement at the end of the aerosol treatment.

Secondary Objectives:

1. To evaluate the proportion of patients who experience a symptomatic improvement at follow up visits (months 3 and 6)
2. To evaluate sinusal pre-chambers (OMC and SER) at the end of the treatment and at follow up visits, versus baseline
3. To evaluate nasal cellularity modification before and after treatment
4. To evaluate the proportion of patients with an improvement of mucociliary clearance after 5 ±2 days from end of treatment
5. To evaluate the proportion of patients with recurrent rhinosinusitis relapses during follow up
6. To evaluate the time from end of treatment to disease exacerbation
7. To evaluate the number of disease exacerbations during the follow up
8. To evaluate ciliary motility by assessing ciliary vitality time with phase contrast microscopy at each visit
9. To evaluate treatment acceptability
10. To evaluate the need of other drugs during follow up period (decongestants, analgesics, anti-inflammatory drugs, other topical steroids).

Study design and Methodology

This was a phase III clinical study, monocentre, randomized, parallel groups, single blind, experimental treatment (flunisolide + NAC) versus active drug (flunisolide + ambroxol).

Four visit were scheduled:

- Basal visit (V1), during which patients were randomized to receive study treatment for 20 days
- A visit after 5 ±2 days from end of treatment (V2) for the evaluation of primary endpoint
- A follow up visit after 3 months ±15 days from end of treatment (V3)
- A follow up visit after 6 months ±15 days from end of treatment (V4)

Each patient had to be treated for a period of 20 days. Follow up period was 6 months after treatment period.

Subject population

Number of Subjects Planned:	150 (75 in each group)
Number of Subjects Randomized:	150 (73 Males/ 77 Females)
Number of Subject Analysed for Safety:	150 (75 in each group).
Number of Subjects Analysed for Efficacy (Intent to treat):	150 (75 in each group)
Number of Subjects Analysed for Efficacy (Per Protocol):	139 (72 in NAC group and 67 in ambroxol group)

Diagnosis and main criteria for inclusions

Diagnosis: recurrent acute rhinosinusitis.

Inclusion criteria. .

1. Male or female
2. Age ≥18 years

Name of Sponsor Company Zambon	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
Name of finished product Fluimucil	PART: [.....]	
Name of active ingredient N-acetylcysteine	VOLUME: [.....]	
	PAGE: [.....]	

3. Patients affected by recurrent acute rhinosinusitis during intercritical phase. Recurrent acute rhinosinusitis was defined according to Lanza and Kennedy classification, requiring the evidence of 4 or more rhinosinusitis exacerbations during one year.

Bacterial etiology was excluded after enrolment by a microbiological test. A positive result to the microbiological test was to be considered as a protocol violation, and the patient was to be dropped out.

Exclusion criteria

1. Hypersensitivity to study compounds or any of the excipients
2. Pulmonary tuberculosis in active or quiescent phase
3. Peptic ulcer
4. Severe hepatic or renal disturbances
5. Bronchial asthma (as principal/primitive affection)
6. Severe cardiovascular diseases
7. Clinically significant metabolic diseases
8. Neoplasms
9. Need for rhinosinusal surgery (for the treatment of chronic, acute or complicated rhinosinusitis, polyposis)
10. Suspected or confirmed active infection
11. Immune system diseases
12. Neuropsychiatric diseases
13. Only for women: suspected or confirmed pregnancy, breast feeding. Women with childbearing potential had to use an efficacious contraceptive system until the end of the follow up period
14. Patients enrolled in other investigational studies in the previous three months
15. Diseases or treatments that could interfere with the evaluation of study treatments
16. Diseases that, in the investigator opinion, could not benefit from any of the treatments under study.

Test product, dose and mode of administration, batch number

	NAC +flunisolide	ambroxol +flunisolide
Dosage	NAC 300 mg + flunisolide 0.1% 2 mL b.i.d.	ambroxol 0 . 75%mL + flunisolide 0,1% 2 mL b.i.d.
Duration of the therapy	20 days	20 days
Mode of administration	aerosol	aerosol
Batch number	PPD	PPD
Expiry date:	PPD	PPD

Criteria for Evaluation

Efficacy

Primary endpoint :

The proportion of patients with a symptomatic improvement at the evaluation performed 5±2 days after the end of treatment (visit 2)

Secondary endpoints:

1. The proportion of patients with a symptomatic improvement at the evaluation performed during visit 3 (3 months ±15 days from the end of treatment) and visit 4 (6 months ±15 days from the end of therapy)
2. The proportion of patients with an improvement in rhinosinusal anatomic evaluation at visits 2, 3 and 4
3. The proportion of patients who score a "success", "mild improvement" and "failure" at the evaluation of the nasal cellularity modification at visits 2, 3 and 4
4. The proportion of patients with disease exacerbation during the follow up, at visits 3 and 4
5. Time to first exacerbation, measured from the end of treatment
6. Ciliary motility, evaluated at each visit
7. Proportion of patients who require the prescription of another drug during the follow up (decongestants, analgesics, anti-inflammatory drugs, other topical steroids, etc)

Safety

1. Drug tolerability: adverse events, physical exam parameters and vital signs were assessed
2. Treatment acceptability: based on the judgement of each patient at the end of treatment
3. Investigator judgement: based on a score assigned from the investigator at the end of treatment and during the following follow up visits.

Statistical methods

Primary analysis: the primary efficacy variable is the proportion of patients with symptomatic improvement (reduction in clinical efficacy score ≥70% versus baseline), at the evaluation performed 5 ±2 days after the end of treatment. The study groups were compared in a chi square test.

Name of Sponsor Company Zambon	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
Name of finished product Fluimucil	PART: [……]	
Name of active ingredient N-acetylcysteine	VOLUME: [……]	
	PAGE: [……]	

Secondary analysis:

Study groups were compared using a chi square test for the following statistics:

- Comparison of the proportion of patients with symptomatic improvement (reduction ≥70%) at 3 and 6 months after the end of treatment was performed by means of a chi square test
- Proportion of patients with improvement in anatomical sinusal (SER, OMC) assessment, proportion of patients with improvement in tubaric function, and with improvement of mucociliary transport
- Proportion of patients who require a second prescription during the follow up
- Acceptability of treatment by the patient, Investigator judgement
- Evaluation of patients about secretion cellularity evaluation.

The number of exacerbations during follow up in patients who responded to the therapy was compared between the two groups in a Wilcoxon test for independent data.

The proportion of patients with disease exacerbations during the follow up was calculated and the groups were compared in a Fisher exact test.

Time to exacerbation was analysed and the groups compared with a Log rank test.

Mucociliary transport time had to be analyzed and the groups compared in a t test.

Safety data: all adverse events were coded according to the MedDRA dictionary. The proportion of patients with each adverse event was calculated. Serious and drug related adverse events were displayed in tables. The physical exam and the vital signs were described per treatment group and visit.

SUMMARY

Efficacy results

Primary endpoint:

All of the 9 symptoms assessed in the clinical efficacy analysis had a severity reduction in both treatment groups. The proportion of patients who scored 0 ("absent") raised from about 30% to 77% and 45% for NAC and ambroxol respectively in pain at the Ewing and Grunwald point, from about 15% to 62.67% and 32% for NAC and ambroxol respectively in nasal obstruction, from about 10% to 50.67% and 22.67% in nasal hyperaemia, from about 60% to 88% and 68% in nasal irritation, from about 32% to 68% and 54.67% in pharyngeal drainage, and from about 65% to 92% and 72% in nasal dryness. In both the ITT and PP population analyses, the patients treated with flunisolide + NAC had a higher symptomatic improvement compared to patients treated with flunisolide + ambroxol: patients who improved were about 66% of subjects treated with NAC and 25% of subjects treated with ambroxol.

The exploratory analysis carried on to assess the proportion of patients with clinical improvement defined as a reduction in symptoms severity of 50% and 40% versus the baseline confirmed the evidence of a significant clinical effect of the flunisolide + NAC treatment.

In the ITT population the proportion of improved patients at the end of treatment was 82.67% versus 50.67 ($p<0.0001$) for the 50% threshold in NAC and ambroxol groups respectively, and 85.33% versus 57.33 ($p=0.0001$) for the 40% threshold in NAC and ambroxol groups, respectively. In the PP population an analogous result was observed: the proportion of improved patients was 83.33% versus 52.24 ($p=0.0001$) for the 50% threshold in NAC and ambroxol groups respectively, and 86.11% versus 59.70 ($p=0.0004$) for the 40% threshold in NAC and ambroxol groups, respectively.

Secondary endpoints:

Clinical condition at follow up: the group treated with flunisolide + NAC had a significantly (chi square $p<0.0001$) greater proportion of patients with symptomatic improvement compared to flunisolide + ambroxol, at both follow up visits in ITT and PP populations (76% versus 33.33% respectively at 1st follow up, and 68% versus 25.33% at 2nd follow up in ITT population).

Rhinosinusal anatomical evaluation: the proportion of patients with an improvement in rhinosinusal districts condition was, in ITT population, 49.33% in flunisolide + NAC group versus 13.33% in flunisolide + ambroxol group at the end of treatment, 60,00% versus 30.67% at the first follow up visit and 58.67% versus 16.00% at the second follow up visit. These results were confirmed in the PP population.

The exploratory analysis showed that the study treatments were significantly different in reducing the severity of rhinosinusal signs assessed by videoendoscopy both at the end of treatment and at the follow up visits. When a severity reduction threshold of 50% was chosen to define the success of the treatment, the proportion of improved patients was 69.33% in the flunisolide + NAC group, and 28% in flunisolide + ambroxol at the end of treatment, 73.33% versus 44% at the first follow up and 74.67% versus 29.33% at the second follow up (ITT population). Clearly, when a 40% threshold was chosen the proportion of patients with improvement rose, but the difference between the treatments remained stable. Analyses performed on the PP population confirmed the results.

Cytological evaluation: the distribution of patients in grading categories was significantly different between the two treatment arms for neutrophils and eosinophils evaluation. The proportion of patients who scored a "success" was greater in the group treated with flunisolide + NAC with respect to the group treated with flunisolide + ambroxol, at each visit in both the ITT and the PP populations (success was reported in 84% of patients in NAC group compared to 64% of patients in ambroxol group at the end of treatment, in ITT population). At the same time the proportion of failures was lower in patients treated with flunisolide + NAC with respect to patients on flunisolide + ambroxol. No other significant differences between treatment groups were observed in the other cytological categories. Anyway, the results of the analysis showed a high

Name of Sponsor Company Zambon	*Individual Study Table referring to the dossier*	*(for National Authority use only)*
Name of finished product Fluimucil	PART: [……]	
Name of active ingredient N-acetylcysteine	VOLUME: [……]	
	PAGE: [……]	

proportion of successes in both groups (about 90% and 80-90% for NAC and ambroxol respectively at all visits for caliciform and metachromatic cells). The analysis of epithelial resulted in a high success rate at all visits in both treatment groups.

Exacerbations: The number of exacerbations observed in the flunisolide + NAC group was significantly lower compared to flunisolide + ambroxol, both at 3 months (8 versus 17 respectively, ITT set) and 6 months (21 versus 60 respectively, ITT set) follow up visits. The number of subjects with at least one exacerbation was significantly lower in the NAC treated group compared to ambroxol, with a >50% reduction at each visit.

The comparison of the median exacerbation time shows that while in the flunisolide + ambroxol group 50% of patients had the first exacerbation at the 158th day of observation, the proportion of patients in the flunisolide + NAC group with an exacerbation was lower than 40% at the end of the follow up period.

Mucociliary motility: mucociliary motility was assessed by measuring ciliary vitality time observed at phase contrast microscopy at each visit. The treatment groups had similar results at baseline (104.7 and 106.6 minutes for flunisolide + NAC and flunisolide + ambroxol respectively). Both treatments caused an increase in cliliary vitality time at the end of treatment, with a significantly better result for the flunisolide + NAC group (ITT population: 138.4 versus 114.3 minutes, NAC and ambroxol respectively; PP population: 140.6 versus 111.8 minutes, NAC and ambroxol respectively). During the follow up, a reduction in vitality time was observed in the flunisolide + ambroxol group (104.6 minutes at visit 3 and 81.8 minutes at visit 4), while the flunisolide + NAC group maintained the therapeutic effect until the last visit of the follow up (147 minutes at visit 3 and 135.2 minutes at visit 4). The study treatment had thus greater efficacy with respect to control treatment in improving patient condition and in maintaining the benefit during time.

Second prescription: the proportion of patients who required a second prescription was lower in flunisolide + NAC arm at both follow up visits, but it reached the statistical significance only after 6 months from the end of therapy (6 versus 14 respectively at 1st follow up, 14 versus 38 respectively at 2nd follow up, ITT set).

Safety results

The proportion of patients with adverse events was lower in the flunisolide + NAC with respect to the flunisolide + ambroxol (18.67% versus 52%, respectively), as was the total number of events observed (16 versus 46, respectively).

With the exception of a general disorder observed in the flunisolide + ambroxol group, all the reported adverse events in both treatment groups were classified as infections or infestations. The only patient who was discontinued from the study (subject PPD) had a PPD , and was excluded from the PP population in accordance to the protocol. In both treatment groups no drug related adverse event was observed.

No patient died. Only one serious adverse event was reported (acute rhinitis), in the flunisolide + ambroxol group, it was judged not drug related.

Patient's acceptability: in the flunisolide + NAC group, 64% of patients rated the acceptability of treatment as "very good", versus 14.67% in flunisolide + ambroxol group. The difference in proportions of patients who judged the treatment negatively was significant as well (1.33% in flunisolide + NAC group, 13.33% in flunisolide + ambroxol group).

Investigator's judgement: the proportion of positive results was greater in flunisolide + NAC group compared to flunisolide + ambroxol group at all timepoints (52% versus 34.04%, 54.67 versus 12%, 61.33% versus 10.67%, respectively). At the same time, the proportion of negative results was greater in the flunisolide + ambroxol group (1.33% versus 10.67%, 0% versus 8%, 1.33% versus 24%, NAC and ambroxol respectively).

Conclusions

As regards the primary efficacy analysis, patients treated with flunisolide + NAC had, at the end of treatment, a clearly greater (more than twice) symptom severity reduction than patients treated with flunisolide + ambroxol.

For what concerns the secondary efficacy analyses, flunisolide + NAC was significantly more efficacious than flunisolide + ambroxol with regard to: symptoms severity reduction at three and six months from the end of treatment; improving anatomical evaluation at all timepoints; determining the success in cytological grading of Neutrophils and Eosinophils; reducing the exacerbations number at three and six months from the end of treatment, and delaying their occurrence; increasing the ciliary vitality time of cells observed in phase microscopy, and maintaining this result during time; reducing the number of following pharmacological prescriptions at six months from the end of treatment. The treatment tolerability with flunisolide + NAC was good: the patients' and Investigator's judgements were very positive, the compliance was high, the number of adverse events was lower than that reported in the flunisolide + ambroxol treatment, and no serious adverse event occurred. Moreover, the treatment was not suspected to be associated with negative or problematic clinical situations, nor any patient required the reduction or the discontinuation of the treatment.

In conclusion, these results confirm that adding NAC to the standard treatment with flunisolide is an efficacious strategy to stop the pathogenetic loop that maintains the condition of recurrent sinusitis, and improve patients' condition, with an effect that lasts for up to six months after the end of treatment.

Date of the report

30 October 2009