- **Protocol number:** Z7244L01
- **Document title:** A Phase III, multi-centre, randomized, rater- and patient blind, placebo- and active-controlled, parallel group clinical trial to compare the safety and efficacy of 1-week treatment with intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese Patients with respiratory tract diseases and abnormal mucus secretions
- **NCT number**: NCT03843541
- **Version number:** 2.0
- **Date of the document**: 19 Dec 2018

CLINICAL TRIAL PROTOCOL

INTRAVENOUS NAC PHASE III CHINA CLINICAL TRIAL (IVNAC-3C)

A PHASE III, MULTI-CENTRE, RANDOMIZED, RATER- AND PATIENT-BLIND, PLACEBO- AND ACTIVE-CONTROLLED, PARALLEL GROUP CLINICAL TRIAL TO COMPARE THE EFFICACY AND SAFETY OF 1-WEEK TREATMENT WITH INTRAVENOUS N-ACETYLCYSTEINE (NAC) 600 MG TWICE DAILY (ACTIVE TEST TREATMENT), AMBROXOL HYDROCHLORIDE 30 MG TWICE DAILY (ACTIVE CONTROL TREATMENT) AND PLACEBO AS EXPECTORANT THERAPIES IN ADULT CHINESE PATIENTS WITHRESPIRATORY TRACT DISEASES AND ABNORMAL MUCUS SECRETIONS

Protocol Code
Z7244L01

Protocol Name
IVNAC-3C (**I**ntra**V**enous **NAC** – Phase **3** **C**hina Trial)

Final Date: 29 August 2018

Version: Version 1.0

Zambon SpA
Via Lillo del Duca 10
20091 Bresso - Milan – Italy

APPROVAL PAGE

Protocol Title: Intravenous NAC Phase III China Trial

A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with respiratory tract diseases and abnormal mucus secretions

Protocol Name: IVNAC-3C (Intra**V**enous **NAC** – Phase **3** **C**hina Trial)

Protocol Code: Z7244L01

Protocol Version and Date: Version 1.0 29 August 2018

Authors: PPD ,

Sponsor Name and Address: Zambon S.p.A.
Via Lillo del Duca 10
20091 Bresso - Milan – Italy

As agreed and approved:

PPD

Date (dd/mm/YYYY)	Global Chief Medical Officer	SIGNATURE

PPD

Date (dd/mm/YYYY)	Global Medical Affairs Head Established & Respiratory Medicines	SIGNATURE

____/____/____	_____	_____
Date (dd/mm/YYYY)	**Principal Investigator**	**SIGNATURE**

ZAMBON CONTACT DETAILS

Zambon S.p.A
Via Lillo del Duca 10
20091 Bresso - Milan (Italy)
Phone: PPD
Email: PPD

Role	Name	Contact Data
Global Medical Affairs Head Established & Respiratory Medicines	PPD, MD, PhD	Phone: PPD PPD
Global Chief Medical Officer	PPD, MD	Phone: PPD PPD
Clinical Project Manager	PPD, PhD	Phone: PPD PPD
Global Head of Drug Safety - Pharmacovigilance contact	PPD, MD	PPD Phone: PPD
Statistician	PPD	PPD Phone: PPD

CONTRACT RESEARCH ORGANISATION CONTACT DETAILS

PAREXEL

Role	Name	Contact Data
Medical Monitor	PPD	PPD Phone: PPD
Contact for serious adverse event/pregnancy reporting	Safety Services Project Leader	PPD
Add others as appropriate		

OTHER INSTITUTIONS

Role	Name	Contact Data
Interactive Web Response System (IWRS)	PPD	PPD
Electronic Data Capture	PPD	PPD Phone: PPD

Role	Name	Contact Data
Investigational Medicinal Product (IMP) Packaging and Labelling;	PPD	PPD Phone: PPD
Investigational Medicinal Product (IMP) Logistic	PPD	PPD Phone: PPD
Add and/or remove as appropriate		

LIST OF COMMITTEES

Not applicable.

SUMMARY OF CHANGES HISTORY

Protocol Version	Key Changes
Protocol Version: Final 1.0	Original Protocol

1. TABLE OF CONTENTS

2. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AH	Ambroxol hydrochloride
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CA	Competent Authority
C-FDA	Chinese Food and Drug Administration
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DV	Deterioration Visit
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EM	Expectation-Maximization
EMA	European Medicines Agency
EoT	End of Treatment
EU	European Union
GCP	Good Clinical Practice
γGT	gamma glutamyl transferase
GSH	Glutathione
HOCl	Hypochorous acid
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ITT	Intention-to-treat
IV	Intravenous
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive Web Response System
Kg	Kilograms
LOCF	Last Observation Carried Forward
MC	Monte Carlo
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mITT	Modified Intention to Treat
ml	Milliliter
MVTF	Missing Value Treatment Failure

NAC	N-acetylcysteine
NaCl	Sodium chloride
PI	Package Insert
PP	Per-protocol population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Traditional Chinese Medicine
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
US-FDA	United States Food and Drug Administration
WHO-DD	World Health Organization-drug dictionary
WOCF	Worst Observation Carried Forward

3. SUMMARY

Title:	**Intravenous NAC Phase III China Trial** A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with respiratory tract diseases and abnormal mucus secretions
Protocol Code/	Z7244L01
Protocol Name:	**IVNAC-3C** (**I**ntra**V**enous **NAC** – Phase **3 C**hina Trial)
Phase:	III
Treatments	**Active test treatment** Ampoule containing 300 mg N-acetylcysteine (NAC) in 3 ml (Zambon Spa, Vicenza, Italy). Two ampoules (NAC 600 mg) in 10 ml NaCl 0.9% saline solution, administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 hours apart for 1 week (7 days). Total daily NAC dose: 1200 mg/day. **Active control treatment** Vial containing 15 mg Ambroxol Hydrochloride (AH) in 2 ml (Boehringer Ingelheim, Shanghai, China***).*** Two vials (AH 30 mg) in 10 ml NaCl 0.9% saline solution administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 hours apart for 1 week (7 days). Total daily AH dose: 60 mg. **Placebo treatment** Vial containing 10ml NaCl 0.9% saline solution (China Otsuka Pharmaceutical Co., Ltd.) One vial of 10 ml NaCl 0.9% saline solution administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 hours apart for 1 week (7 days).

Objectives:	**Efficacy objectives** **Primary objective** Demonstrate that slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score in adult Chinese hospitalized patients with respiratory tract diseases and abnormal mucus secretions **Secondary objectives** **Efficacy objectives** Demonstrate in the same patient population that: - slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to day 3 and end of 1-week treatment of other indicators of mucolytic activity (individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume); - slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is non-inferior to slow intravenous infusion of ambroxol hydrochloride 30 mg twice daily in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score; - slow (at least 5 minutes) intravenous infusion of ambroxol hydrochloride 30 mg twice daily is superior to placebo in change from baseline to day 3 and to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score and of other indicators of mucolytic activity: individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume. **Safety objectives** - Confirm that 1-week treatment with iv NAC 600 mg twice daily is safe and well tolerated.
Design:	Multicenter, randomized, rater- and patient-blind, placebo- and active-controlled, 3-arm parallel group clinical trial. Subjects will be randomized to NAC or ambroxol or placebo in a 1:1:1 ratio. The study will consist of a total of 4 core hospital visits and a follow-up call 2 weeks after end of treatment. If the patient is still hospitalized or if more convenient for the patient, the follow-up phone call can be replaced by a follow-up hospital visit.
Number of patients:	A total of 333 patients will be randomized. This number includes 10% overage to allow for patients who discontinue the trial prematurely (“drop-outs”) without contributing to the primary end-point.

Trial duration:	Approximately 8 months. The enrolment period will be approximately 7 months.
Duration of patient participation:	Up to 4 weeks. Each patient will undergo a screening period of up to 1 week, a 1-week treatment period and a 2-week follow-up period.
Participating Countries:	China
Number of Sites:	Approximately in the range of 15-25
Population:	**Inclusion criteria** Patients will be enrolled in the trial if all of the following criteria are met: 1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as : acute bronchitis, chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis Chinese ethnicity and/or Chinese 2. Signed the informed consent form before any study-related procedure 3. Sputum viscosity score ≥ 2 at randomization visit 4. Expectoration difficulty score ≥ 2 at randomization visit 5. Willingness and ability to comply with study procedures **Exclusion criteria** Patients will not be enrolled if one or more of the following criteria are met: 1. Intolerance or contra-indication to treatment with NAC or ambroxol or allergy to any component of the study treatments 2. (For female patients) ongoing pregnancy or lactation, or childbearing potential but unwillingness to adopt abstinence or contraception measures during the study 3. Intake of an investigational drug within 1 month before the screening visit 4. Use of expectorants or drugs with expectorant effect within 3 days before randomization visit 5. Medical history of and/or illness (including laboratory abnormality) and/or treatment that in the investigator's opinion may interfere with the patient's safety, compliance, or study evaluations 6. Serum ALT and/or AST more than 3 times above the upper limit of normal at screening visit 7. Serum creatinine more than 3 times above the upper limit of normal at screening visit

8. Addiction to alcohol or drugs
9. Mental illness, or other reasons for non-cooperation in the investigator's opinion

Outcome measures:

Efficacy variables

- Sputum viscosity, expectoration difficulty, sputum color and cough are assessed by means of ordinal categorical 4-point scales with 0 = best and 3= worst.
  For each patient the assessment is to be carried out by the blinded rater on treatment days 1 (baseline), 3 and 7 in the morning between 7 am and 9 am before administration of study drug. Should a patient discontinue prematurely from the trial (including discharge from the hospital before day 7) an assessment should be conducted on the day of discharge whenever possible.
  Scoring criteria are as follows:

	0	1	2	3
Sputum viscosity	Liquid (normal viscosity)	Fluid (mildly increased viscosity)	Viscous (moderately increased viscosity)	Sticky (severely increased viscosity)
Expectoration difficulty	No difficulty	Mild difficulty	Moderate difficulty	Marked difficulty
Sputum Color	Mostly white	Mostly pale yellow	Mostly dark yellow	Very dark yellow /green
Cough	No cough	Sporadic and mild cough	Moderate cough	Severe Cough

Adapted from [12].

- Sputum volume: patients will collect 24-hour sputum (morning to same time of the following morning) in a graduated cup on treatment days 1 (Baseline), 3 and 7. Volume will be expressed as mL/24h.

Safety variables

- Adverse events assessed for severity and seriousness.
- Laboratory measurements including hematology, liver enzymes, serum creatinine.
- 12-lead electrocardiogram

End-points:

Primary efficacy end-point

Superiority of NAC over placebo in change from baseline to end of 1-week treatment of mean sputum viscosity score or mean expectoration difficulty score.

The study will be declared success if at least one of two components of the primary end-point will show superiority over placebo.

Secondary efficacy end-points

A. Superiority of NAC over placebo:

- in change from baseline to day 3 of mean sputum viscosity score OR mean expectoration difficulty score;
- in change from baseline to day 3 and to end of 1-week treatment of individual scores:
  - mean sputum viscosity score
  - mean expectoration difficulty score
  - mean sputum color score
  - mean cough score
- in change from baseline to day 3 and to end of 1-week treatment of mean sputum volume

B. Non-inferiority of NAC vs. ambroxol in change from baseline to end of 1-week treatment of mean sputum viscosity score or change of mean expectoration difficulty score.

C. Superiority of ambroxol vs. placebo in change from baseline to day 3 and to end of 1-week treatment of
  - mean sputum viscosity score OR mean expectoration difficulty score;
  - mean sputum viscosity score (individual score)
  - mean expectoration difficulty score (individual score)
  - mean sputum color score
  - mean cough score
  - mean sputum volume

Safety end-points

Counts and frequency distributions of

- all, mild/moderate/severe, non-serious/serious adverse events
- vital signs
- Laboratory tests
- 12-lead ECG (normal, abnormal clinically non- significant, abnormal clinically significant)

Statistical Analysis:

Sample size justification

This study has been powered to reach statistical significance for the superiority comparisons of N-acetyl-cysteine (NAC) vs. placebo (primary study objective), and for the non-inferiority comparisons of NAC vs. ambroxol hydrochloride (secondary study objective) in at least one of the two co-primary endpoints at the end of the 1-week treatment. To control the overall type I family-wise error rate at the one-tailed 0.025 significance level, a multiple-sequence gatekeeping procedure was implemented in a Monte Carlo study with 1000 runs and with the Bonferroni correction applied to the set of superiority comparisons (first gatekeeper) and the Hochberg correction applied to the set of non-inferiority comparisons (second gatekeeper).

For the superiority tests, and with group sample sizes of 100 patients in placebo group and 100 patients in NAC group, the Monte Carlo study estimated an overall power ("disjunctive" power) close to 93% to reach statistical significance in at least one co-primary end-point. These calculations are based on a one-sided Mann-Whitney test and assuming a minimal clinically relevant difference of 0.35 points between placebo and NAC on a 0-3-point scale, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two end-points equal to 0.31.

For the non-inferiority tests, a sample of 100 patients per each active treatment group ensures sufficient disjunctive power (Monte Carlo disjunctive power = 82%) to detect non-inferiority between NAC and ambroxol in at least one co-primary end-point. These calculations are based on a one-sided non-inferiority t-test assuming a margin of non-inferiority equal to 0.30, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two endpoints equal to 0.31.

Assuming a drop-out rate of about 10% over one week of entry, a total of 333 patients will be randomized (i.e. 111 patients in the placebo group, 111 patients in the NAC group and 111 patients in the ambroxol group).

Statistical methods

All efficacy analyses will be performed on the Modified Intention to Treat (mITT) population. Analysis of the primary and secondary efficacy variables will be also carried out on the Per Protocol (PP) population to assess the robustness of the findings. Safety outcomes will be analysed on the Safety population.

The primary efficacy end-points "change from baseline to the 1-week treatment in sputum viscosity score and change from baseline to the 1-week treatment in expectoration difficulty score" will be analysed by means of conventional Mann-Whitney U Statistic for testing the hypotheses of superiority of NAC versus placebo and by means of the non-inferiority variant of the Mann-Whitney U Statistic for testing the hypotheses of non-inferiority of

NAC versus ambroxol. Statistical significant results will be needed on both mITT and PP populations to accept the hypothesis of non-inferiority of NAC versus ambroxol. Point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

The overall type I family-wise error rate for testing the co-primary endpoints in superiority and non-inferiority assessments will be controlled at the one-tailed 0.025 significance level using a multiple-sequence gatekeeping procedure. This procedure will be fully described in the protocol.

The same approach will be taken for the supportive secondary end-point "superiority of NAC over placebo in change from baseline to day 3 of mean sputum viscosity score or mean expectoration difficulty score".

As for the supportive secondary efficacy end-points concerning individual scores (sputum viscosity, expectoration difficulty, sputum colour, cough) or measured on continuous scale (sputum volume), the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (Mann-Whitney U Statistic), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

The same statistical analysis (Mann-Whitney Test) will be carried out for testing superiority of ambroxol vs placebo on the same efficacy endpoints. Results will be used for the purpose of verifying study's assay sensitivity.

For the analyses of supportive secondary efficacy end-points no adjustment of significance level will be made to account for multiple comparisons.

Missing data on the primary and secondary efficacy endpoints will be imputed as treatment failures (MVTF) by replacing missing values using the worst observation carried forward (WOCF) as primary imputation method (namely baseline or follow-up measurement, whichever is worse, and using expectation-maximization (EM) algorithm and last observation carried forward (LOCF) as sensitivity analyses.

Concomitant Treatments

Permitted

- Appropriate treatment(s) for any respiratory tract disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes, such as: corticosteroids (inhaled or systemic),

bronchodilators, antibiotics (in case of co-administration, the i.v. antibiotic should be administered separately).

- Appropriate treatment(s) for any other underlying disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes
- If co-treatment with parenteral nitroglycerin is needed the patients should be monitored for potential hypotension, which may be severe and may be indicated by the presence of headache
-
- If one or more treatments interfering with the measurements contributing to the primary efficacy outcomes are deemed necessary, the patient should not be randomized or should be discontinued from the study.

Not permitted

- Expectorants
- Antitussive agents
- Sedatives
- Traditional Chinese Medicine (TCM) treatments.

4. INTRODUCTION AND RATIONALE

Background

Numerous respiratory diseases, including acute and chronic bronchitis, COPD, cystic fibrosis and non-cystic fibrosis bronchiectasis are characterized by increased sputum viscosity and difficult expectoration, often associated with cough (1- 4).

Furthermore, acute and chronic bronchitis and COPD are commonly associated with of many non-respiratory chronic conditions in both outpatients and hospitalized patients, especially in smokers, elderly patients and patients living in heavily polluted environments.

In China, cigarette smoking, and high environmental pollution have a high prevalence and morbidity (5). Hence, abnormalities of mucus and expectoration are frequent in patients with primary respiratory diseases and with respiratory complications of chronic non-respiratory conditions (6).

Treatment

Mucolytic agents are used worldwide for symptomatic treatment of abnormalities of mucus viscosity and expectoration. These include N-acetyl cysteine, also referred to as NAC (Fluimucil®, Zambon) and ambroxol hydrochloride (Mucosolvan®, Boehringer Ingelheim; Fluibron®, Chiesi Farmaceutici S.a.s.).

NAC exerts an intense mucolytic-fluidifying action on mucous and mucopurulent secretions by depolymerizing mucoproteic complexes and nucleic acids which contribute to the viscosity of sputum and other secretions. In addition, NAC exerts a direct antioxidant action, thanks to its free thiol (-SH) nucleophilic group which can interact with the electrophilic groups of oxidant radicals. Of interest is the finding that NAC protects α1-antitrypsin, an elastase-inhibiting enzyme, from inactivation by hypochlorous acid (HClO), a potent oxidant agent produced by the myeloperoxidase enzyme of activated phagocytes. Moreover, NAC can easily cross the cellular membranes; inside the cell NAC is deacetylated to L-cysteine, an amino acid indispensable for glutathione (GSH) synthesis. GSH, a highly reactive tripeptide found in many animal tissues, is the most important endo-cellular protective agent against oxidant radicals, exogenous and endogenous, as well as against several cytotoxic substances (7)

NAC is approved in China for aerosol administration (8) and broadly used by this route of administration as mucolytic agent. However, especially in hospital settings, in China there is a preference to use mucolytic agents by intravenous administration in patients with moderate to severe abnormalities of mucus viscosity and expectoration: intravenous administration is considered by hospital staff more convenient due to common use of other intravenous treatments and is preferred by patients. Hence, the lack of approved NAC for intravenous administration in China is an important gap in medical practice.

Intravenous administration of NAC is approved in most countries at very high doses as an antidote against liver injury due to paracetamol intoxication (see Section 5) (9) and in several countries, namely as mucolytic agent (10). More detail is provided in the Investigator Brochure (IB).

The efficacy and safety of iv infusion of NAC as mucolytic was investigated in seven clinical trials, 3 of which randomized and controlled (11-13) and 4 uncontrolled (14-17).

Trial Rationale

This trial is intended to provide pivotal (phase III) evidence of efficacy and safety for registration in China of slow intravenous infusion of NAC in adult hospitalised patients with with respiratory tract diseases and abnormal mucus secretions.NAC, the active test treatment, will be compared to placebo and to ambroxol hydrochloride. The inclusion of a placebo arm is deemed ethically and scientifically sound for the following reasons: 1) the selection criteria used in this study ensure that condition being studied is not serious or life threatening at the time of enrolment; 2) immediate discontinuation from the trial and rescue use of mucolytics is envisaged in the protocol; 3) the true value of iv intervention in the target population is not fully established. The use of placebo was

requested by the Chinese FDA (C-FDA) reviewers in their feedback to an earlier version of this protocol. Ambroxol hydrochloride is included as the third treatment arm of the study as it is the only mucolytic agent approved in China for iv administration. The inclusion of an active control arm, also requested by C-FDA reviewers, will allow to test internal validity of the trial.

This trial is designed as rater- and patient-blind. i.e. whereas the staff administering the study drugs will know what each patient is receiving, neither the staff evaluating the patient, nor the patients themselves will know. The trial cannot be fully blinded (double-blind) because the appearance of NAC ampoules and ambroxol vials is different and more importantly because the NAC formulation releases a harmless but immediately distinguishable sulfuric smell. Rater- and patient-blinded designs are accepted for pivotal registration trials by the US-FDA, EMA and Regulatory Authorities worldwide in situations where full blinding is impossible.

The selected doses of iv NAC and ambroxol are within the limits of relevant SmPCs (10,18); dose justification is provided in Section 5 below.

The treatment duration of 1 week has been selected after consultation with Chinese experts, as only a small minority of patients receive iv mucolytics for more than 1 week.

5. EVALUATION OF THE ANTICIPATED RISKS/BENEFIT RATIO

NAC has been available to patients as a mucolytic agent for many years and has a well-established and satisfactory safety and tolerability profile (see IB).

Independently of route of administration (inhalation, oral, intravenous) adverse events are reported rarely following NAC administration and are usually mild and transient.

The most frequent adverse events associated with NAC oral administration are gastrointestinal (e.g., vomiting, diarrhoea, stomatitis, abdominal pain and nausea). Hypersensitivity reactions (e.g. anaphylactoid reactions, urticaria, rash, pruritus, and bronchospasm) have been reported less frequently after oral administration, while with the IV administration they were reported more frequently compared to gastrointestinal symptoms. Some of the hypersensitivity reactions were associated to higher infusion rate. Most anaphylactoid reactions can be managed by temporarily suspending the acetylcysteine infusion, administering appropriate supportive care. A cumulative analysis of all safety reports received by the Sponsor up to September 2017 for NAC IV, confirmed the nature and severity of the events were in line with the above profile of the product.

Intravenous NAC has been studied in clinical trials and published case series both as mucolytic agent and as an antidote against intoxication by paracetamol and other toxic agents including amanita phalloides and chlorinated hydrocarbons. Overall, in published studies in humans, a total of 745 patients were exposed to iv NAC at doses ranging from 500 mg/day to 980mg/kg/day for a duration of 1 to 18 days. Details of safety results are included in the IB.

In published studies, whereas iv NAC as mucolytic agent typically was given at doses up to 1000 mg/day, much higher iv doses of NAC as antidote were given over multiple days, maintaining a satisfactory safety profile.

Locatelli and colleagues (19) published two case series, one of 86 patients with acute intoxication from amanita phalloides and the other of 35 patients with acute intoxication from chlorinated hydrocarbons. Patients received iv NAC 300 mg/kg/day for 3 to 14 days and 3 to 18 days respectively. The safety and tolerability profile were overall benign, with 4 out of 121 exposed patients suffering from anaphylactoid reaction or rash (due to the rapid administration of the bolus

according to the authors), none of which caused discontinuation of treatment. No other AEs were reported.

Keays and colleagues (20) randomized 50 patients suffering from paracetamol intoxication and admitted to the liver failure unit to NAC in addition to conventional intensive liver care (N=25) or conventional intensive liver care alone (N=25) with maintenance dose of 100 mg/kg/day for several days, until recovery from encephalopathy or death (the average number and range of treatment days is not reported but in survivors appears to be at least 4 days). No AEs were reported in the patients treated with NAC.

From the data summarized above and the full dataset summarized in the IB, a daily intravenous dose NAC of 1200 mg/day given in a hospital setting for 7 days is likely to be associated with a small safety risk.

The safety profile of the active comparator ambroxol hydrochloride given intravenously as is also favourable, as outlined in the Chinese PI. The product is well tolerated, and mild upper gastrointestinal adverse reactions have been occasionally reported, mainly including stomach burning, indigestion and occasional nausea and vomiting, occurring mostly after parenteral administration. Allergic reactions are rare, mainly including rash. Few cases have reported severe acute allergic reactions, but the correlation with ambroxol hydrochloride is not known. The dose chosen for this trial (60 mg/day) is within the range allowed by the Chinese SmPC (18).

Anticipated benefits to the patients with respiratory tract diseases and abnormal mucus secretions randomised to NAC and ambroxol hydrochloride include reduction in mucus viscosity and improved expectoration.

In conclusion, for both active treatments, in this trial the benefit risk ratio is anticipated to be positive.

Patients randomized to placebo will be monitored very closely by experienced investigators and study staff. Should expectoration difficulty increase during the trial, the investigator and/or the patient may choose to discontinue the study treatment and immediately administer/receive rescue mucolytic, as described in Sections 8.1 and 10.10. Hence, also for the patients randomized to placebo no clinically meaningfully negative benefit/risk ratio is anticipated.

6. OBJECTIVES

The primary objective of this trial is to demonstrate that slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score in adult Chinese hospitalized patients with respiratory tract diseases and abnormal mucus secretions .

Secondary objectives are as follows:
Efficacy
Demonstrate in the same patient population that:
- slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to day 3 and end of 1-week treatment of other indicators of mucolytic activity: individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume;
- slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is non-inferior to slow intravenous infusion of ambroxol hydrochloride 30 mg twice daily in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score;
- slow (at least 5 minutes) intravenous infusion of ambroxol hydrochloride 30 mg twice daily is superior to placebo in change from baseline to day 3 and to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score and of other indicators of mucolytic activity:

individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume.
Safety
Confirm that 1-week treatment with iv NAC 600 mg twice daily is safe and well tolerated

The trial endpoints are described in Section 20.2.

7. ETHICS REQUIREMENTS

This trial will be conducted in compliance with last version of Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html), with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), in particular E6(R2), with the applicable regulatory requirements and with Zambon and contract research organisation (CRO) standard operating procedures (SOPs).

8. DESIGN AND DURATION OF THE CLINICAL TRIAL

8.1. CLINICAL TRIAL DESIGN

This is a multicenter, randomized, rater- and patient-blind, placebo- and active-controlled, 3-arm parallel group clinical trial.

The trial will be conducted in approximately 15 -25 sites in China.

Please refer to Appendix 1 for a trial flow chart.

The study will consist of a total of 4 core hospital visits (screening, baseline, treatment day 3, treatment day 7, see Section 9) and of one follow-up phone call 2 weeks after discontinuation of treatment; if the patient is still hospitalized or if more convenient for the patient, the follow-up phone call can be replaced by a follow-up hospital visit.

At screening visit (Visit 1), patients will be asked to provide Informed Consent prior to any trial related procedure and will be checked against inclusion and exclusion criteria. Their medical history will be recorded. Furthermore, patients will undergo a 12-lead ECG and laboratory assessments. Results must be available before Visit 2.

At randomization visit (Visit 2), to occur within 7 days after Visit 1, female patients will undergo a pregnancy test; all patients will be checked again against the full set of inclusion and exclusion criteria and eligible subjects will be randomised with a 1:1:1 ratio to receive NAC or ambroxol hydrochloride or placebo.

A total of 111 patients are to be randomized in each treatment group.

Procedures performed at each core hospital visit will include documentation of concomitant medications and treatment emergent adverse events (TEAEs), 24-hour sputum collection and assessment on a 4-point ordinal scale of expectoration difficulty, sputum viscosity, sputum colour and cough.

In case a patient experiences a deterioration of expectoration capacity and related symptoms, and/or of an underlying condition, he/she should contact a study investigator immediately and undergo an unscheduled deterioration visit. If the patient and/or the investigator believe that it is in the patient's best interest to receive a rescue mucolytic, the patient will be discontinued from the study and rescue mucolytic will be administered, with any additional treatment the investigator deems appropriate.

8.2. DURATION OF CLINICAL TRIAL

The overall study duration (from first patient first visit to last patient last visit) is expected to be of approximately 8 months.

The maximum expected duration of participation in this trial for an individual subject, from Visit 1 (Screening) to the follow-up phone call or visit is 4 weeks. Treatment duration will be 1 week (7days).

The start of the trial is defined as first subject in, i.e. Visit 1 for the first subject.

The end of the trial is defined as the last subject out, i.e. when the last subject had the follow-up phone call or follow-up visit or unscheduled Deterioration visit.

If the trial is prematurely stopped, please refer to Section 16.

9. CLINICAL TRIAL POPULATION

9.1. NUMBER OF SUBJECTS

A total of 333 subjects (111 in each treatment group) is planned to be enrolled into the trial. The enrolment is competitive among sites.

For a description of sample size calculation, please refer to Section 20.3.

9.2. SELECTION OF SUBJECTS

9.2.1. INCLUSION CRITERIA

Subjects can be enrolled in the trial if they meet all inclusion criteria listed below:

1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as : acute bronchitis , chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis Chinese ethnicity and/or Chinese
2. Signed the informed consent form before any study-related procedure
3. Sputum viscosity score ≥ 2 at randomization visit
4. Expectoration difficulty score ≥ 2 at randomization visit
5. Willingness and ability to comply with study procedures

9.2.2. EXCLUSION CRITERIA

Subjects are not eligible for the trial if they meet one or more of the exclusion criteria listed below:

1. Intolerance or contra-indication to treatment with NAC or ambroxol or allergy to any component of the study treatments
2. (For female patients) ongoing pregnancy or lactation, or childbearing potential but unwillingness to adopt abstinence or contraception measures during the study
3. Intake of an investigational drug within 1 month before the screening visit
4. Use of expectorants or drugs with expectorant effect within 3 days before randomization visit

5. Medical history of and/or illness (including laboratory abnormalities) and/or treatment that in the investigator's opinion may interfere with the patient's safety, compliance, or study evaluations
6. Serum ALT and/or AST more than 3 times above the upper limit of normal at screening visit
7. Serum creatinine more than 3 times above the upper limit of normal at screening visit
8. Addiction to alcohol or drugs
9. Mental illness, or other reasons for non-cooperation in the investigator's opinion

Contraceptive methods

Although teratology studies carried out in animals evidenced no teratogenic effects of NAC (ref IB) or ambroxol hydrochloride (ref SmPC Italy), safety in human pregnancy has not been established with iv administration.

Female subjects can be enrolled if they are either post-menopausal for at least 2 years, or surgically sterilized or have undergone hysterectomy.

Female subjects of child-bearing potential must be willing to avoid pregnancy. They are required to have a negative pregnancy test at inclusion (see Section 10.2), and should use a highly effective method of birth control for 1 month prior to randomisation, throughout the trial duration and up to 1 month after the last dose of IMP, which include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- surgical sterilization (e.g. bilateral tubal ligation or occlusion)
- male sterilization (vasectomised partner)
- sexual abstinence
- a male sexual partner who agrees to use a male condom with spermicide

Throughout the course of the study male participants with female partners of child bearing potential must abstain from sexual intercourse or use condoms or use effective contraceptive precautions (female partners should follow the same birth control of female patients).
Male participants must also not take part in the donation of sperm whilst enrolled on the study.

10. OVERALL CLINICAL TRIAL SCHEDULE

The current trial will include 4 planned core clinical visits at the investigational site and 1 follow-up telephone call or visit. Unscheduled Deterioration visit(s) will be conducted as necessary. A detailed flow chart showing the procedures performed is given in Appendix 1. The following sections outline the procedures to be performed at the individual visits.

10.1. VISIT 1 - SCREENING VISIT

At Visit 1 (Screening), the following procedures will be performed:

- obtain written Informed Consent before any study-related procedure;

- document medical history and subject's demographic data;
- document concomitant medications;
- assess vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- conduct 12-lead ECG in the supine position after 5 minutes of rest (Section 11.1.6);
- check inclusion/exclusion criteria: not all criteria can be assessed at screening, but do not proceed further if the patient is not eligible based on the criteria that can be checked;
- collect blood samples for clinical laboratory assessments (haematology and clinical chemistry). (Section 11.1.4);
- Instruct patients on actions to be taken in case of worsening of symptoms related to expectoration.
- Record details of any AEs since the Inform Consent signature

The Investigator will arrange an appointment for Visit 2 within 7 days.

10.2. VISIT 2 - RANDOMISATION VISIT (DAY 1)- (WITHIN 7 DAYS OF VISIT 1)

At Visit 2 (Randomisation), the following procedures will be performed:

- conduct dip-stick urine pregnancy test for females of childbearing potential.
- check complete set of inclusion and exclusion criteria;
- document concomitant medications;
- record details of any AEs since the Screening Visit (Visit 1);
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- give to patient the container for 24-hour sputum collection and instruct patient to collect all sputum until the same time of the following day;
- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided;
- randomise the eligible patient by IWRS;
- administer first dose of study medication in the morning and the second dose in the afternoon/evening. The two daily doses must be administered approximately 12 hours apart from each other.
  Warning: Study staff responsible for administration of study medication, patient care and routine assessments (unblinded) should be different from study staff responsible for rating of expectoration difficulty, sputum viscosity, sputum color and cough (rater). No disclosure of the identity of study medication from the former to the latter is to occur unless required for safety reasons;
- remind patients on actions to be taken in case of worsening of symptoms related to expectoration.
- To assess adherence with IMP dosing regimen

The Investigator will arrange an appointment for Visit 3 (on day 3 after Visit 2) and will instruct the subjects to report any AEs occurring during this period at the next visit.

10.3. DAY 2

On day 2 the following procedures will be performed:

- collect 24-hour sputum sample and report volume (mL) in eCRF;
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

10.4. VISIT 3 (DAY 3)

At Visit 3 (day 3), the following procedures will be performed:

- document concomitant medications;
- record details of any AEs since the Randomization Visit (Visit 2);
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- give to patient the container for 24-hour sputum collection and instruct patient to collect all sputum until the same time of the following day;
- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above);
- remind patients on actions to be taken in case of worsening of symptoms related to expectoration. To assess adherence with IMP dosing regimen

The Investigator will arrange an appointment for Visit 4 (on day 7 after Visit 2) and will instruct the subjects to report any AEs occurring during this period at the next visit.

10.5. DAY 4

On day 4 the following procedures will be performed:

- collect 24-hour sputum sample and report volume (mL) in eCRF;
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

10.6. DAYS 5 AND 6

On days 5 and 6 the following procedure will be performed:

- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

10.7. VISIT 4 (DAY 7)

At Visit 4 (day 7), the following procedures will be performed:

- conduct dip-stick urine pregnancy test for females of childbearing potential.
- document concomitant medications;
- record details of any AEs since Visit 3 (day 3);
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- give to patient the container for 24-hour sputum collection and instruct patient to collect all sputum until the same time of the following day;
- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided.
- conduct 12-lead ECG in the supine position after 5 minutes of rest (Section 11.1.6);
- collect blood samples for clinical laboratory assessments (haematology and clinical chemistry).
- to assess adherence with IMP dosing regimen
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

The Investigator will arrange an appointment for the follow-up call or visit 2 weeks ± 3 days after the last administration of IMP

10.8. DAY 8

On day 8 the following procedure will be performed:

- collect 24-hour sputum sample and report volume (mL) in eCRF;

10.9. FOLLOW-UP PHONE CALL OR VISIT (2 WEEKS ± 3 DAYS AFTER THE LAST ADMINISTRATION OF IMP)

A follow-up phone call will be performed at 2 weeks ± 3 days after the last administration of IMP. If the patient is still hospitalized or it is more convenient for the patient, the follow-up call can be replaced by a follow-up visit

The following procedures will be performed during the follow-up call or visit:

- record details of any AEs since Visit 4 (day 7);
- record concomitant medications since Visit 4.

10.10. UNSCHEDULED DETERIORATION VISIT

Patients will be trained by the Investigator to recognise worsening of expectoration and related symptoms.

If the patient and/or the investigator believe that it is in the patient's best interest to receive a rescue mucolytic, the patient will be discontinued from the study and rescue mucolytic will be administered, with any additional treatment the investigator deems appropriate and an unscheduled Deterioration Visit should be conducted whenever possible.

An unscheduled Deterioration Visit should be conducted also in case of worsening of the underlying condition. In particular, in case of bronchospasm in asthmatic patients the treatment must be discontinued and adequate therapeutic measures taken.

In case of unscheduled Deterioration Visit the following procedures will be performed:

- record details of any AEs since previous visit
- conduct dip-stick urine pregnancy test for females of childbearing potential.
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- conduct 12-lead ECG in the supine position after 5 minutes of rest (Section 11.1.6);
- conduct assessment of expectoration difficulty, sputum viscosity, sputum colour and cough by means of the 4-point ordinal scales provided

In case during the unscheduled deterioration visit the patient and/or the investigator deem appropriate the discontinuation from the trial, all evaluations requested at Visit 4 should be performed (Section 10.11).

10.11. PREMATURE DISCONTINUATION VISIT

In case of premature discontinuation for any other reasons than those listed in 10.10 all evaluations requested at Visit 4 should be performed, excluding study medication administration.

A premature discontinuation visit must also be conducted in case of unexpected pregnancy.

11. METHODOLOGY

11.1. METHODS OF ASSESSMENT

11.1.1. DEMOGRAPHY AND MEDICAL HISTORY

At Visit 1 (Screening) the subjects' demographic data will be documented, including age, ethnicity, gender, height, weight as well as smoking history and alcohol use.

Further, the reason for hospitalization and medical history will be documented.

Any relevant worsening in ongoing conditions during the trial (i.e. since Visit 1) is required to be recorded as AEs in the eCRF (see Section 18).

11.1.2. PHYSICAL EXAMINATION

At Visit 1, Visit 2, Visit 3 and Visit 4, and/or at the unscheduled deterioration Visit/premature discontinuation, a physical examination of general body systems will be performed according to current medical standards and site practice. The examination is to include a chest auscultation. Any relevant worsening regarding physical examination results of a subject since Visit 1 should be recorded as AE in the eCRF (see Section 18).

11.1.3. VITAL SIGNS

At Visit 1, Visit 2, Visit 3 and Visit 4 and/or at the unscheduled deterioration visit/premature discontinuation, vital signs will be recorded according to site practice. Vital signs include:

- heart rate,
- systolic and diastolic blood pressure, measured after at least 5 minutes in the supine position,
- respiratory rate,
- body temperature, measured under the arm pit.

Automatic or manual devices may be used, but the same device should be used for any given subject throughout the trial. The same arm should be used for all measurements.

Any relevant clinically significant worsening of vital signs of a subject since the previous visit should be recorded as AE in the eCRF (see Section 18).

11.1.4. LABORATORY EVALUATIONS

Routine laboratory evaluations will be performed at Screening Visit (Visit 1) and Visit 4 and in case of premature discontinuation.

The blood samples must be collected after the 12-lead ECG has been performed.

The haematology and clinical chemistry parameters detailed in Table 1 will be analysed by the local hospital laboratory.

Subjects with clinically relevant impaired renal function, as defined by serum creatinine levels ≥3.0x upper limit of normal at Visit 1 will not be randomized.

Subjects with clinically relevant impaired liver function, as defined by serum ALT and/or AST ≥3.0x upper limit of normal at Visit 1 will not be randomized.

A dipstick urine pregnancy test for women of childbearing potential will be performed at Randomization Visit (Visit 2) and at Visit 4 and/or at unscheduled deterioration visit/premature discontinuation visit.

Female subjects who become pregnant during the trial must be withdrawn from the trial without delay and undergo the premature discontinuation visit; these patients are to be followed up to determine the outcome of the pregnancy. The Investigator is required to inform the Sponsor of a subject's pregnancy and the estimated date of delivery. Reporting requirements are outlined in Section 18.10.

Clinical laboratory tests will be reviewed for results of potential clinical significance before Visit 2 to confirm patient's eligibility and during the trial, as appropriate. Clinically significant laboratory abnormalities arising at Visit 4 (or at premature discontinuation visit) are considered AEs. Where possible, a diagnosis should be ascribed to the abnormal lab test.

Table 1 CLINICAL LABORATORY EVALUATIONS

Hematology: at Screening Visit (Visit 1) and Visit 4 or premature discontinuation visit			
Hematocrit	Hemoglobin	Platelet count	Red blood cell count
White blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils)			
Clinical Chemistry: at Screening Visit (Visit 1) and visit 4 or premature discontinuation visit			
BUN or UREA	Chloride	AST	
Creatinine	Uric acid	ALT	
Sodium	Amylase	γGT	
Potassium	ALP	Bilirubin (direct and total)	
Calcium			
Pregnancy Test: at Screening Visit (Visit 1), Visit 4 or premature discontinuation visit			
Urine β-hCG (dipstick)			

11.1.5. EFFICACY EVALUATIONS

Sputum viscosity, expectoration difficulty, sputum color, cough

Sputum viscosity, expectoration difficulty, sputum color and cough are assessed by means of ordinal categorical 4-point scales with 0 = best and 3 = worst.

For each patient the assessment is to be carried out by the blinded rater on treatment days 1 (baseline), 3 and 7 in the morning before 9 am before administration of study drug. Should a patient discontinue prematurely from the trial (including discharge from the hospital before day 7) an

assessment should be conducted on the day of discontinuation whenever possible (see unscheduled Deterioration Visit, Section 10.10).

Scoring criteria are as follows (adapted from [12])

	0	1	2	3
Sputum viscosity	Liquid (normal viscosity)	Fluid (mildly increased viscosity)	Viscous (moderately increased viscosity)	Sticky (severely increased viscosity)
Expectoration difficulty	No difficulty	Mild difficulty	Moderate difficulty	Marked difficulty
Sputum color	Mostly white	Mostly pale yellow	Mostly dark yellow	Very dark yellow /green
Cough	No cough	Sporadic and mild cough	Moderate cough	Severe Cough

Sputum Volume

At Randomization Visit (Visit 2), Visit 3 and Visit 4 the patients will be given a graduated container and instructed to use it to collect all sputum generated in the following 24 hours (i.e. same time of the following day). The day the container will be collected, and the 24-hour sputum volume measured in ml.

11.1.6. SAFETY EVALUATIONS

Adverse Events

AEs will be recorded by Investigator in the appropriate eCRF Section from Visit 1 (date of informed consent) to the follow-up phone all or visit occurring 2 weeks (±3 days) after the last administration of the investigational medicinal product (IMP). At each contact (i.e. clinical visit or phone call), subjects will be asked in a non-leading manner if they experienced any AEs.

All AEs occurring from the day of the first IMP administration, i.e. Visit 2, until the end of the trial, i.e. follow-up phone call, will be considered as treatment emergent TEAEs.

For definitions and reporting of AEs and SAEs, see Section 18.

12-lead electrocardiogram (ECG)

12-lead ECG recordings will be obtained at each study centre using site machines at the Screening Visit (Visit 1) to verify the eligibility of the subject, and at Visit 4 or unscheduled Deterioration visit.

ECG will be performed after obtaining vital signs. Prior to recording, the subject should be at rest for at least 5 mins.

ECG will be evaluated by the investigator/local medical staff and the recording will be reported in the eCRF as “normal”, “abnormal clinically significant” or “abnormal not clinically significant”.

Abnormalities of clinical significance recorded at V1, Visit 4 or unscheduled deterioration visit/premature discontinuation visit which are not related to pre-exist medical condition before ICF signature will be reported as AEs. Repeat measurements will be performed if needed.

11.2. ADHERENCE WITH IMP DOSING REGIMEN

As the administration of the IMP will be carried out by the study staff in a hospital setting, it is anticipated that adherence with IMP dosing regimen will be high.

Nevertheless, the Investigator will assess adherence with IMP dosing regimen on an ongoing basis by determining the amount of IMP dispensed, used (i.e. returned open ampoules/vials) and the amount of IMP returned (i.e. returned, unopened ampoules/vials) at Visit 2 (first dose), Visit 3 and Visit 4 (end of treatment) or unscheduled Deterioration Visit/premature discontinuation visit.

The evaluation of compliance will be done using the following formula:

$$\% \text{ of administered drug} = 100 \times \frac{\text{Total number of administered doses}}{\text{Total number of scheduled doses}}$$

11.3. PHARMACODYNAMICS

Not applicable.

11.4. PHARMACOKINETICS

Not applicable.

12. PRIOR AND CONCOMITANT TREATMENTS

At Visit 1 (Screening), all prior and concomitant medications, including antibiotics, and over-the-counter products used by an individual subject within 1 month prior to Screening Visit (Visit 1) will be documented in the eCRF.

During all subsequent clinical visits, the Investigator will document any changes in concomitant medications.

The following concomitant treatments are permitted from Visit 1 to Visit 4 (end of IMP treatment) or unscheduled Deterioration Visit:

- Appropriate treatment(s) for any underlying disease, that in the investigator’s opinion will not interfere with the measurements contributing to the primary efficacy outcomes. If one or more treatments interfering with the measurements contributing to the primary efficacy outcomes are deemed necessary, the patient should not be randomized or should be discontinued from the study.

The following concomitant treatments are not permitted from Visit 1 to Visit 4 (end of IMP treatment) or unscheduled Deterioration Visit:

- Expectorants
- Antitussive agents
- Sedatives
- Traditional Chinese Medicine (TCM) treatments.

13. INVESTIGATIONAL MEDICINAL PRODUCT

13.1. INVESTIGATIONAL MEDICINAL PRODUCT SUPPLIES AND PACKAGING

NAC will be supplied in boxes containing 2 ampoules each.

NAC is formulated in yellow glass ampoules as a solution of 300 mg NAC in 3 ml water for injection; other excipients are: sodium hydroxide and disodium edetate. The product is manufactured by Zambon SpA, Vicenza, Italy.

Ambroxol hydrochloride will be supplied in boxes containing 2 vials each.

Ambroxol hydrochloride is formulated in yellow glass vials as a solution of 15 mg ambroxol hydrochloride in 2 ml water for injection; other excipients are: citric acid monohydrate, sodium hydrogen phosphate dihydrate, sodium chloride. The product is manufactured by Boehringer Ingelheim.

Placebo will be supplied in boxes containing 1 vial each.

Placebo is formulated in vials as 10 ml NaCl 0.9% saline solution. The product is manufactured by China Otsuka Pharmaceutical Co., Ltd.

13.2. INVESTIGATIONAL MEDICINAL PRODUCT DISPENSING AND ADMINISTRATION

All IMPs will be administered at the hospital investigational sites by study staff otherwise not involved with the assessment and care of study patients. The study staff members administering the IMP will be aware of its identity but will not disclose it to patients or to other study staff members (patient and rater-blind design, see Section 4).

NAC (Active test treatment)

Two ampoules (NAC 600 mg) will be diluted in 10 ml NaCl 0.9% saline solution and administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 ± 1 hours apart for 1 week (7 days). Total daily NAC dose: 1200 mg/day.

Ambroxol hydrochloride (active control treatment)

Two vials (ambroxol 30 mg) will be diluted in 10 ml NaCl 0.9% saline solution and administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 ± 1 hours apart for 1 week (7 days). Total daily ambroxol dose: 60 mg.

Placebo

One vial of 10 ml NaCl 0.9% saline solution will be administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 ± 1 hours apart for 1 week (7 days).

Study staff administering the IMP will be instructed to store the empty used and the unused ampoules/vials for IMP accountability.

13.3. RANDOMISATION

Each subject will receive a screening number as soon as site staff enters the IWRS, after they have signed the ICF (Visit 1).

The screening number will consist of country number (3 digits), a site number (3 digits) and a continuous number for a subject at an individual site (3 digits), e.g. 001001-001. Every subject who signs the ICF must be entered into the IWRS system regardless of eligibility.

At Visit 2, eligible subjects will be randomised using the IWRS according to a pre-specified randomisation scheme such that they either receive NAC or ambroxol hydrochloride or placebo.

The randomisation within each site will be done with blocks sized of unequal length to guarantee a good balance among NAC, ambroxol hydrochloride and placebo at any stage of the enrolment minimizing the procedure selection bias.

The allocation to the treatment will be stored within the IWRS database until unblinding of the trial is requested. Unblinding may be performed directly by the Investigators only in case of SAE of life-threating significance where knowledge of treatment assignment is essential for the future management of patient care (see Section 15.1).

13.4. INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

IMP inventory and accountability records will be maintained within IWRS. The following rules are to be followed:

a) The Investigator will keep IMPs in a pharmacy, or a locked and secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the IMPs.

b) The inventory will be maintained by the Investigator or pharmacist or other nominated individual. The inventory will be done by means of a specific “Subject/Study Investigational Product Accountability Record & Investigational Product Reconciliation Log” and will include details of IMPs received and a clear record of when they were dispensed.

c) At the conclusion or termination of the clinical trial, the Investigator will conduct a final IMP inventory and to record the results of the inventory on an Investigational Product Return Form. The monitor will check that IMP accountability was correctly performed. The Investigator will return all original IMP containers, whether empty or full, to the CRO for final reconciliation and destruction.

d) The Investigator/pharmacist agree not to supply IMP to any person except those named as Investigators/Co-Investigators as detailed in the Site Signature/Delegation Log, and to subjects in this trial.

For instructions to maintain the study patient and rater-blind, see Section 4.

14. CLINICAL TRIAL AMENDMENTS

Changes to the CTP can be made preparing written amendments to be agreed and signed by the Principal Investigator and Sponsor. No substantial amendment can be implemented without a favourable opinion of the Ethics Committee (EC) and Competent Authority (CA) and CA, unless the changes consist of urgent safety measures to protect trial subjects.

Amendments which are non-substantial amendments as defined by current regulations can be sent to EC/CA for notification as applicable per local requirements and may be implemented at the site before EC notification according to local rules.

15. DEVIATIONS FROM THE CLINICAL TRIAL PROTOCOL

Any major or critical deviation which may have an impact on study results and/or the safety of the subjects should be immediately reported to the CRO and a decision will be taken together with the Sponsor whether or not the patient for whom the deviation from the CTP took place is to continue in the trial. A deviation log will be maintained to track actual deviations and decisions taken. All deviations will be reported to the EC and CA according to ICH-GCP and local requirements.

In case of an emergency deviation from the CTP has to be implemented for a give patient, this deviation will be only applied to that individual.

In such an emergency the Investigator must contact the CRO by telephone as soon as possible.

15.1. CODE BREAKING

The code for any individual subject will not be broken by the Investigator/rater during course of the trial except in the circumstance of an SAE where knowledge of treatment assignment is essential for the future management of patient care.

Despite the fact that this study is not double-blind, in order to ensure proper documentation, in case of emergency, unblinding of the treatment is to be done through IWRS. The IWRS will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the site users. Site users will be provided with usernames and passwords to access the IWRS. Unblinding of the study treatment must be done in case of an emergency situation, where the Investigator/rater considers it essential to know what treatment the subject was taking. Access to the unblinding option will be granted only to the Investigators and sub-Investigators at the sites. The IWRS will promptly notify the Sponsor and the Clinical Trial Monitor whenever a treatment code is unblinded. If the treatment code has been opened, this must be recorded in the eCRF.

Users from PAREXEL and Sponsor Pharmacovigilance will have their own passwords to unblind subjects in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the CA and ECs.

16. CLINICAL TRIAL WITHDRAWALS/DROP-OUTS

Patients will be withdrawn from the trial for one of the following reasons:

- patient may withdraw from the study at any time at his/her own request;
- patient may withdraw from the study due to an AE;
- patient may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative reasons;
- patient may be withdrawn due to lack of adherence to study medication regimen.

- Female patient who becomes pregnant should be withdrawn from the trial and followed-up in accordance with Section 18.8;
- Patient should be withdrawn from the trial once rescue mucolytic is received;
- non-emergency unblinding of study treatment allocation;
- lost to follow up: before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study;

The sponsor, CA, or EC/IRB(s), can terminate the trial or participation of an individual site.

The reason for removal of a subject from the trial or premature discontinuation of treatment must be fully documented in the eCRF as well as in respective source documents. Follow-up for withdrawn subjects follows the procedures described in Section 18.8 and Section 18.9.

17. STOPPING AND DISCONTINUATION CRITERIA FOR THE TRIAL

The trial may be prematurely terminated or placed on temporary hold for the following reasons:

- the Sponsor feels that the number and/or severity of AEs justifies discontinuation of the trial;
- the Sponsor considers the applied doses of one or more IMPs to be no longer relevant;
- data not known before, become available and raise concern about the safety of one or more IMPs so that continuation would pose potential risks to the subjects;

Premature termination of the trial must be reported to the EC and CA according to applicable laws generally within 30 days. A detailed written explanation of the reason should be given and alternative procedures for subjects under treatment specified.

However, trial results have to be reported according to the requirements outlined in this CTP as far as applicable.

If, after the termination of the trial, the risk/benefit analyses have changed, the new evaluation should be provided in case it will have an impact on the planned follow-up of the patients who have participated in the trial. If possible, the patients should return to the clinic for an early End of Treatment Visit.

18. REPORTING SAFETY INFORMATION

18.1. DEFINITION OF ADVERSE EVENT

An AE is "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".

AEs include:

- worsening (change in nature, severity or frequency) of conditions present at the onset of the trial;
    - worsening of expectoration difficulties and related symptoms may prompt discontinuation of the patient and immediate administration of rescue mucolytic if

judged to be in the patient's best interest by the investigator and/or the patient him/herself

- subject deterioration due to the primary illness;
- intercurrent illnesses;
- drug interactions;
- events related or possibly related to concomitant medications;
- abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the IMP.

An unscheduled Deterioration Visit should be conducted whenever possible (Section 10.10).

18.2. DEFINITION OF ADVERSE EVENT OF SPECIAL INTEREST

No AEs of special interest are defined for this trial.

18.3. DEFINITION OF ADVERSE DRUG REACTION

An adverse drug reaction (ADR) is "any untoward and unintended response to an IMP related to any dose administered and which implies an AE with at least a reasonable possibility of a causal relationship with the use of the product (i.e. there is evidence or arguments to suggest a causal relationship).

The definition covers also medication error and uses outside what is foreseen in the CTP, including misuse and abuse of the IMP.

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

18.3.1. DEFINITION OF UNEXPECTED ADVERSE DRUG REACTION

An unexpected ADR is: "An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure [IB] for an unapproved investigational product or SmPC, for approved product)". The reference safety information for evaluation of AE expectedness in this trial will be the Investigator Brochure for NAC and the Chinese Package Insert for ambroxol hydrochloride.

18.3.2. DEFINITION OF MEDICAL DEVICE MALFUNCTION AND INCIDENT

A medical device malfunction is the failure of a device to meet performance specifications or to perform as intended.

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, a user, or other persons, or to a serious deterioration in their state of health.

A medical device complaint meeting the criteria of a potential medical device incident is reportable.

Subjects will also be monitored for any medical device malfunction or incident and, if these occur, details will be recorded as for ADRs.

18.4. DEFINITION OF SERIOUS ADVERSE EVENTS OR SERIOUS ADVERSE DRUG REACTIONS

18.4.1. DEFINITION OF SERIOUS ADVERSE EVENT OR SERIOUS ADVERSE REACTION

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening (i.e. the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement);
- is a congenital anomaly/birth defect;
- is an important medical event that may not result in death, be life-threatening, or require hospitalisation but, according to appropriate medical judgment, it may jeopardise the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

A Serious Adverse Reaction (SAR) is any SAE judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product.

18.4.2. DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs/SARs that, although foreseeable, are potentially related to the IMP and not identified in the reference safety information and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

18.5. DEFINITION OF SEVERITY OF ADVERSE EVENTS

The term “severe” is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the subject may experience slight discomfort;
- Moderate: causing some limitation of usual activities; the subject may experience annoying discomfort;
- Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

18.6. DEFINITION OF ADVERSE EVENT CAUSALITY

Causality shall be determined according to the definition of ADRs as given in Section 18.3.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as ADRs. The causality assessment given by the Investigator should not be downgraded by the Sponsor.

The following binary decision for causality will be used:

- reasonable possibility that the IMP caused the event;
- no reasonable possibility that the IMP caused the event.

Features supportive of an association include:

- temporal plausibility;
- pharmacological properties of the drug or of the substance class;
- course of the AE after de-challenge and, if applicable, after re-challenge;
- specific tests indicating involvement of the drug in the occurrence/worsening of the AE;
- alternative explanations.

18.7. ADVERSE EVENT RECORDING

Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the IMP, must be recorded by the Investigator on the AE information page of the eCRF. Also, for SAEs, information must be recorded in the eCRF (see Section 19.1).

The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF.

18.8. ADVERSE EVENT MONITORING WINDOW

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: final study visit/ETV (observation window)

An AE occurring after the final visit/ETV and coming to knowledge of the investigator (e.g. during a follow-up assessment or by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator's judgment.

18.9. ADVERSE EVENT REPORTING

The Investigator must report to the CRO all AEs which occur during the trial, regardless of their relationship to IMP. All AEs are recorded by the Investigator on the AE information page of the eCRF.

In addition, any SAE will have to be reported according to the following detailed procedure.

18.9.1. REPORTING SERIOUS ADVERSE EVENTS

Investigators must report SAEs **within 24 hours of first awareness of the event**.

The SAE must be reported through the eCRF to the CRO's Pharmacovigilance group as per contact details provided in the "List of CRO personnel" at the beginning of this CTP.

If there is any issue with the electronic reporting process, such as internet failure or database issues, this must not delay SAE reporting. The back-up procedure is to send the back-up paper

Serious Adverse Event Form to the CRO's Pharmacovigilance group by email or fax using the contact details specified in the SAE guidelines.

Note: Any reports submitted on paper must be retrospectively added to the eCRF as soon as possible.

The national and local standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

SAEs are reportable from the time a patient signs the informed consent to the follow-up phone call or visit occurring 2 weeks (± 3 days) after the last dose of IMP.

If the Investigator becomes aware of any SAE occurring to a subject within the follow-up window established in this CTP, he/she will report the SAE as above. The SAE will be also reported in the eCRF.

If the Investigator becomes aware of any SAE outside the follow-up window established in this CTP, it is the Investigator's responsibility to report the SAE to the CRO. The Investigator might use the eCRF, as described above. However, the SAE is not an event occurred within the trial period.

18.9.2. REPORTING ADVERSE EVENTS OF SPECIAL INTEREST

No specific provisions relate to reporting of AEs of special interest in this trial.

18.10. FOLLOW-UP FOR ADVERSE EVENTS

All AEs requiring the subject's discontinuation and SAEs will be followed up until they are resolved or closed.

Resolution of an AE is defined as the return to pre-treatment status or stabilisation of the condition with the expectation that it will remain chronic.

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) and answer any question that the Sponsor or designee may have regarding the AE.

Regarding SAEs, the timelines and procedure for follow-up reports are the same as those for the initial reports for SAEs.

This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

If follow-up information on SAEs is available, a follow-up eCRF form will be filled-in by the Investigator and sent to the CRO as above-described, under Section 18.8.1.

18.11. PREGNANCY

Subjects must be instructed that known or suspected pregnancy occurring during the trial should be confirmed and reported to the Investigator, who must then withdraw the subject from the trial without delay (Section 10.10). The Investigator should also be notified in case the partner of a male study subject becomes pregnant at any time during the course of the study (in this event a specific ICF for the subject's partner will be obtained).

In the event that a subject or a female partner is found to be pregnant after inclusion in the trial, then pregnancy will be actively followed up to term and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the CRO.

The Investigator will send pregnancy reports within the timeframes of SAEs.

If pregnancy results in abnormal outcome that the Investigator and/or the Sponsor considers to be due to the IMP, this will be treated as an expedited ADR report.

19. RECORDS

19.1. CASE REPORT FORMS, SOURCE DATA AND QUERY RESOLUTION

The Investigator must ensure that the clinical data required by the CTP are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the official files (source documentation).

Data entered directly into the eCRF comprises all data raised via the 4-point ordinal scales for the assessment of expectoration difficulty, sputum viscosity, sputum color and cough and the 24-hour sputum volume.

ECG and laboratory results must be printed and signed by the Investigator and kept as source data on site after entering outcome into the eCRF.

All other data has to be documented in the subject file as source data first and then entered into the eCRF.

Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a subject visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by trial monitors for completeness and acceptability during monitoring visits.

If data correction is required for an eCRF after initial entry, the site personnel can make necessary corrections on their own or as a response to an automated query by the eCRF system. Monitor and Clinical Data Manager review the eCRF for accuracy and can also generate queries to the investigational staff for resolution.

Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

19.2. RECORDS MAINTAINED BY THE INVESTIGATOR

A copy of all trial records (any documents sent or received from the Sponsor/CRO, correspondence with EC and any other institution or authority and relevant approvals, subjects' source data and subjects' identification documentation) must be maintained by the Investigator for at least 5 years, or for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the Investigator.

19.3. TRIAL MASTER FILE

The Trial Master File (TMF) will be maintained by the CRO according to the respective CRO SOPs with direct access for all study participants.

At the end of the trial, the TMF will be transferred to the Sponsor, where it will be archived according to specific Sponsor SOPs. A copy of the Investigator files will be left on site after trial end.

19.4. TRIAL MONITORING

The trial will be monitored by means of regular visits and telephone calls according to specific and pre-defined SOPs and trial specific monitoring guidelines. Details of the visits will be recorded in appropriate Monitoring Report forms to be submitted regularly to Sponsor. Any relevant protocol deviation must be promptly communicated to designated Sponsor's personnel

Monitoring will be performed by personnel of the CRO, Parexel.

19.5. CONFIDENTIALITY OF SUBJECT'S INFORMATION

The Investigator has the responsibility to maintain the pseudonymity of subjects in compliance with the Chinese and Italian data protection laws. In all trial documents, subjects are associated to a code which does not reveal subject's identity. Only at the site, the Investigator holds the subject's identity on a Subject Identification Log under his/her responsibility. The Investigator will maintain this for the longest period allowed by his/her own institution and, in any case, until further communication from the Sponsor.

The site and the Sponsor shall process personal data of subjects involved in the clinical trial as data controllers and in compliance with the Italian data protection law, each of them in its area of competence and in accordance with the responsibilities provided by GCP, only in relation to the trial performance and for pharmacovigilance purposes.

Any contracted organisation as data processor including Parexel, the local laboratories, and IWRS provider, will act in compliance with the terms and conditions agreed with the Sponsor.

20. BIOMETRICS

20.1. DATA MANAGEMENT

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at Parexel.

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- eCRF and Electronic Data Capture (EDC) system – data capture
- Statistical Analysis System (SAS®) – statistical review and analysis
- Pharmacovigilance safety database

Subject data will be captured in an eCRF system and reviewed by the Clinical Research Associate in order to check CTP adherence and to detect any data inconsistency or discrepancy (data validation step).

Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version current at trial start and which will be maintained during the trial.

Previous and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Actual versions of coding dictionaries used will be stated in the CTR.

The final data file will be transferred to the Sponsor in the agreed format as soon as possible after the trial is completed.

20.2. STUDY END-POINTS

Primary efficacy end-point

Superiority of NAC over placebo in change from baseline to end of 1-week treatment of mean sputum viscosity score or mean expectoration difficulty score.

The study will be declared success if at least one of two components of the primary end-point will show superiority over placebo.

Secondary efficacy end-points

A. Superiority of NAC over placebo

- in change from baseline to day 3 of mean sputum viscosity score OR mean expectoration difficulty score;
- in change from baseline to day 3 and to end of 1-week treatment of individual scores:
  - mean sputum viscosity score
  - mean expectoration difficulty score
  - mean sputum color score
  - mean cough score
- in change from baseline to day 3 and to end of 1-week treatment of mean sputum volume

D. Non-inferiority of NAC vs. ambroxol in change from baseline to end of 1-week treatment of mean sputum viscosity score or change of mean expectoration difficulty score.

E. Superiority of ambroxol vs. placebo in change from baseline to day 3 and to end of 1-week treatment of

- mean sputum viscosity score OR mean expectoration difficulty score;
- mean sputum viscosity score (individual score)
- mean expectoration difficulty score (individual score)
- mean sputum color score
- mean cough score
- mean sputum volume

Safety end-points

Counts and frequency distributions of

- all, mild/moderate/severe, non-serious/serious adverse events
- vital signs
- Laboratory tests
- 12-lead ECG (normal, abnormal clinically non-significant, abnormal clinically significant)

20.3. SAMPLE SIZE

This study has been powered to reach statistical significance for the superiority comparisons of N-acetyl cysteine (NAC) vs. placebo (primary study objective), and for the non-inferiority comparisons of NAC vs. ambroxol hydrochloride (key secondary study objective) in at least one of the two co-

primary endpoints at the end of the 1-week treatment. This implies that sample size computation must account for the type I error inflation caused by the multiplicity over the two co-primary endpoints and by the multiplicity over the study targets (superiority and non-inferiority assessments) as well as the logical relationships among the two family of hypotheses with the non-inferiority testable only provided that the superiority contrast, assessed on the same endpoint, is statistical significant. To accomplish this, a multiple-sequence gatekeeping procedure [21] was implemented in a Monte Carlo (MC) study with 1000 runs and with the Bonferroni correction applied to the set of superiority comparisons (first gatekeeper) and the Hochberg correction applied to the set of non-inferiority comparisons (second gatekeeper) in order to control the overall type I family-wise error rate at the one-tailed 0.025 significance level. Details on the adopted gatekeeping strategy are reported further on.
For the superiority tests, and with group sample sizes of 100 patients in placebo group and 100 patients in NAC group, the Monte Carlo study estimated an overall power ("disjunctive" power) close to 93% to reach statistical significance in at least one co-primary end-point. These calculations are based on a one-sided Mann-Whitney test and assuming a minimal clinically relevant difference of 0,35 points between placebo and NAC on a 0-3-point scale, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two end-points equal to 0.31.
For the non-inferiority tests, a sample of 100 patients per each active treatment group ensures sufficient disjunctive power (Monte Carlo disjunctive power = 82%) to detect non-inferiority between NAC and ambroxol in at least one co-primary end-point. These calculations are based on a one-sided non-inferiority t-test assuming a margin of non-inferiority equal to 0.30, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two endpoints equal to 0.31.

Assuming a drop-out rate of about 10% over one week of entry, a total of 333 patients will be randomized (i.e. 111 patients in the placebo group, 111 patients in the NAC group and 111 patients in the ambroxol group. The sample size calculations were performed using the Mediana package [22].

20.4. STATISTICAL ANALYSES

20.4.1. GENERAL STATISTICAL CONSIDERATIONS

All data captured on eCRFs will be available as listings.

The statistical analysis will be performed by the CRO and it will be carried out according to ICH guidelines ICH E9: "Statistical Principles for Clinical Trials" (CPMP/ICH/363/96). If not otherwise stated all statistical analyses and data tabulations will be produced using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA).

The data from all sites will be pooled. Unless stated otherwise, all available data from withdrawn subjects will be included in the analysis up to the time of withdrawal.

The primary study objective will be assessed by testing superiority of NAC compared to placebo and will be achieved if at least one of the two co-primary end-points will be found statistically significant. The key secondary objective will be assessed through the analysis of non-inferiority of NAC compared to ambroxol and, similarly, will be reached if at least one of the two co-primary end-points will be found statistically significant. Conversely, the analyses on the remaining secondary

efficacy endpoints will be treated as non-key secondary objectives since they will be performed only to support primary endpoints findings.

All tests will be one-sided and performed at the significance nominal level of $\alpha = 0.025$. Details are reported in Section 20.4.5.

More detail about the statistical analysis will be provided in the SAP. The SAP will be released before the start of the study. Any change in the SAP occurred after release will be documented as an amendment. Any deviation from the SAP occurring after breaking the blind will be documented and justified in the final CTR and deviations will be clearly marked as 'post hoc' analyses.

20.4.2. TRIAL POPULATIONS

There will be 4 analysis populations defined for the trial analyses:

Intention-To-Treat (ITT) Population The Intention-To-Treat Population will include all subjects who provided informed consent and received a patient number (randomisation number) whether or not they receive IMP.

Modified Intention-To-Treat Population The Modified ITT (mITT) Population will comprise all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.

Primary analyses will be performed on the mITT population with exclusions from the ITT defined and justified in the SAP.

Following the ITT principle, subjects will be analysed according to the treatment they have been assigned to at randomisation.

The mITT will be used to produce summaries of baseline subject characteristics and for the analysis of all efficacy endpoints.

Safety Population

The Safety Population will comprise all subjects who provide Informed Consent and received at least 1 dose or partial dose of IMP.

Subjects will be analysed according to the treatment they actually received.

The Safety Population will be used to produce summaries of all safety related endpoints and demography.

Per-protocol Population

The Per-protocol Population (PP) will include all mITT subjects who were compliant with study drug administration (i.e. had a compliance of at least 80%) and who had no major protocol deviations that were considered as potentially impacting the efficacy results. Major protocol deviations might include, but are not be limited to, subjects taking a not-permitted concomitant medication, the IMP not being administered during the trial as defined in the protocol, subjects receiving a treatment different than the one assigned by randomisation; others will be defined in the SAP.

With the exclusion of non-inferiority comparisons, results of the primary and secondary efficacy endpoints analyses conducted in the PP will be considered as supportive.

Exclusion of subjects from the PP analyses will be decided jointly by the CRO and Sponsor's Medical Monitor, Clinical Trial Manager and Statistician prior to unblinding of the randomisation code and database release.

The subjects or observations to be excluded, and the reasons for their exclusion will be documented and approved by the above-mentioned persons prior to database release. The documentation will be filed together with the remaining trial documentation.

The number of subjects in each analysis population will be reported. Violations excluding subjects from any particular population will be described, reporting the number of protocol violators per each criterion. All protocol violations, minor ones included, will be listed.

20.4.3. EFFICACY DATA

If not otherwise stated the mITT population will be used for the primary analyses of each of the efficacy endpoints whilst results from supplemental analyses using the Per Protocol Population will be compared to those based on the mITT population to assess the effects of dropouts, missing data and exclusions for protocol violations.

The distributions of all the efficacy endpoints listed in Section 20.2 will be summarized by treatment group and time point. Counts and percentages will be reported with the latest computed based on the numbers of patients with non-missing observations. The percentages will be suppressed when the count is zero in order to draw attention to the non-zero counts. Furthermore, efficacy endpoints will be further summarized by arithmetic means, standard deviations, medians quartiles, minima and maxima.

20.4.3.1. ANALYSIS OF PRIMARY END-POINTS

The co-primary efficacy endpoints are: “the change from baseline to the 1-week treatment in sputum viscosity score” and “the change from baseline to the 1-week treatment in expectoration difficulty score” and will be analyzed on the mITT and PP populations by means of conventional Mann-Whitney U Statistics for testing the hypotheses of superiority of NAC versus placebo (primary objective)) and by means of a modified Mann-Whitney U Statistics [23] for testing the hypotheses of non-inferiority of NAC versus ambroxol (key secondary objective) assuming a margin of non-inferiority equal to 0.30. Statistical significant results will be needed on both mITT and PP populations to accept the hypothesis of non-inferiority of NAC versus ambroxol. Point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

20.4.3.2. ANALYSIS OF SECONDARY ENDPOINTS

- Change from baseline to day 3 in sputum viscosity score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (Mann-Whitney U Statistics), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 in expectoration difficulty score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (Mann-Whitney U Statistics), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 and to the end of the 1-week treatment period in sputum color score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (Mann-Whitney U Statistics), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 and to the end of the 1-week treatment period in cough severity score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (Mann-Whitney U Statistics), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

- Change from baseline to day 3 and to the end of the 1-week treatment period in sputum volume: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (Mann-Whitney U Statistics), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

The same statistical analysis (Mann-Whitney Test) will be carried out for testing superiority of ambroxol vs. placebo on the same efficacy endpoints. Results will be used for the purpose of verifying study's assay sensitivity.

20.4.4. HANDLING OF MISSING DATA

Missing data on the primary and secondary efficacy endpoints will be imputed as treatment failures (MVTF) by replacing missing values with the scores recorded at baseline or last measurement, whichever is worse as primary imputation method. Expectation-maximization (EM) algorithm and last observation carried forward (LOCF) will also be used as sensitivity analyses. Details regarding the EM algorithm (i.e. the randomization seed and the SAS code that will be used) will be reported in the SAP.

20.4.5. MULTIPLICITY

The overall type I family-wise error rate will be preserved at the one-tailed 0,025 nominal level (i.e. $\alpha = 0,025$) by controlling multiplicity over the two co-primary endpoints and over the two study targets (superiority and non-inferiority) using a multiple-sequence gatekeeping procedure [20]. To achieve this, the analyses on primary endpoints will be grouped into two family of comparisons (gatekeepers) and processed as follows:

1. The first gatekeeper includes the superiority contrasts "NAC vs placebo" with the adjustment for multiple comparisons across the two co-primary endpoints performed according to Bonferroni. This implies that a difference will be considered statistically significant for a one-tailed p-value ≤ 0.0125 (i.e. $\alpha/2 = 0.0125$). The transition to the second gatekeeper requires that at least one of the two co-primary endpoints is statistically significant.
2. The second gatekeeper includes the family of non-inferiority contrasts "NAC vs ambroxol". The analyses in the second gatekeeper will be performed depending upon the results obtained in the first gatekeeper as shown below:
    a. If both superiority contrasts will be found statistically significant, non-inferiority will be tested on both co-primary endpoints with an overall probability α set to 0,025 (one-tailed) and with the adjustment for multiple comparisons across the two co-primary endpoints performed according to Hochberg.
    b. If only one of the two superiority contrasts will be found statistically significant, non-inferiority will be tested only for that co-primary endpoint and will be considered achieved if the associated one-tailed p-value will be ≤ 0.0125.

Consistent with the hypothesis testing process performed on the co-primary endpoints, the strategy described above will also be applied to control the coverage of confidence intervals at the two-tailed 95% nominal level (i.e. $1 - 2\alpha = 0,95$).

The analyses on secondary efficacy endpoints (not key) will be performed only to support primary endpoints findings and/or for explorative reasons, therefore no adjustment of significance level will be made to account for multiple comparisons.

20.4.6. MULTICENTER STUDY

As additional analysis, a test of site-by-treatment interaction will be carried-out using a two-way nonparametric ANOVA performed by resorting to the “Aligned Rank Transform” (ART) procedure [24]. The interaction will be considered statistically significant for a two-tailed α=0.1. Also, in order to graphically assess the possible heterogeneity of the treatment effect across centres, forest plots will be generated to display the results at each center. In case that the number of patients in each site were scarce, sites will be gathered into “region”. Upon completion of the study and prior to unblinding, study statisticians in consultation with the clinical team will determine the pooling based on enrolment numbers and geographical proximity.

20.4.7. INTERIM ANALYSES

No interim analyses are planned.

20.4.8. SAFETY DATA

All safety endpoints will be summarised and analysed using the Safety Population.

Incidence of Treatment Emergent Adverse Events

The number and the percentage of subjects reporting TEAEs, treatment emergent SAEs, severe TEAEs, TEAEs leading to discontinuation and TEAEs leading to death will be presented by treatment group, along with the number of events occurring.

TEAEs will be summarised also by System Organ Class and Preferred Term according to MedDRA; they will be additionally summarised by severity and relationship to treatment. A separate summary table will be provided for SAEs.

Only TEAEs, i.e. events with an onset date on or after the date of IMP start, will be included in the summary tables. Individual data listings will include all AEs recorded; a separate listing will be provided for treatment-emergent SAEs.

Vital Signs

Descriptive statistics for vital signs will be presented overall and by treatment.

Physical examination data.

Descriptive statistics for physical examination data will be presented overall and by treatment.

Haematology and clinical chemistry

Haematology and clinical chemistry tests results will be converted to standard international units and summarised by treatment group using descriptive statistics for continuous variables. Summaries for change from Visit 1 will be also provided. Frequency of subjects with values appearing outside the central laboratory normal range will be reported by visit for each treatment group. All values appearing outside the laboratory normal range will be highlighted in listings.

12-lead Electrocardiogram

Descriptive statistics for ECG results will be presented overall and by treatment (normal, abnormal clinically non-significant, abnormal clinically significant).

Adherence and Exposure

Subject adherence will be summarised by treatment group presenting descriptive statistics and percentages of adherent subjects, i.e. with a least 80% of compliance.

The total number of doses of IMP taken by each subject, will be summarised as well.

If an AE has a partial or fully missing date, and it is unclear whether the AE is treatment-emergent, it will be assumed that it is. In the AEs analysis, when relationship to study drug is missing for a

treatment-emergent adverse event it will be imputed to be drug related. More detail will be provided in the Statistical Analysis Plan (SAP).

21. INFORMED CONSENT

Written informed consent will be obtained by the Investigator or other authorized person from all subjects or their legally acceptable representative.

The Investigator is responsible for correctly obtaining the informed consent in accordance with the applicable regulatory requirement(s), GCP and the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, the Investigator should have received the EC written approval of the ICF.

Informed consent must be obtained prior to the initiation of any procedures specific to the trial. The record of the informed consent must be available to be audited/inspected by the Sponsor/CRO designees and by CA(s), whenever requested.

The informed consent documentation must be personally dated and signed by the trial subjects, to confirm that consent is based on information that has been understood, and by the Investigator.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

Before informed consent may be obtained, the Investigator or other authorised person, should provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject.

The subject should receive a copy of the signed and dated ICF and any other written information provided to him/her, and updates.

If the subject is not able to write, a verbal consent can be obtained. For illiterate patients, at least 1 impartial witness must be invited to join in the consent process, who would sign off ICF.

Further, in case the subject and his/her legal representative are unable to read, informed consent will be obtained in the presence of an impartial witness, i.e. a person independent of the trial who will read the ICF and the written information for the subject.

22. ETHICS COMMITTEE APPROVAL

This trial will be undertaken only after written and dated approval from EC has been received by the Investigator and by the Sponsor for CTP, all its appendices, ICF, and subjects recruitment procedures (i.e. advertisement) if applicable.

In addition to the above-mentioned documents, the EC will be provided with an updated Investigator Brochure, SmPc and IMPD (where applicable), the Investigator's up-to-date Curriculum Vitae and/or other documentation evidencing qualifications, and any other documents that the EC may need to fulfil its responsibilities.

During the trial, on regular basis, the Investigator will have to submit written summaries of the trial status (i.e. recruitment rate) to the EC, if requested.

23. REGULATORY REQUIREMENTS

The trial is to be conducted in compliance with the Chinese legislation and ICH-GCP E6 Rev2.

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Selection of subjects will not start prior to the approval of the EC has been obtained and the trial notified to or authorised by CAs as per national and local requirements.

24. QUALITY ASSURANCE

This CTP has been audited by the Sponsor's Quality Assurance. The Audit Plan for the study includes site audits. Audits will be planned and conducted according to the Sponsor's SOPs.

25. INSURANCE

The Sponsor is concerned with the safety of the subjects in the clinical trial and wishes to protect the Investigator (and as applicable per local regulations, the site, the monitor and all the Investigator's staff involved in the trial) in the event of claims or lawsuits alleging injury as a result of administration of a study drug.

In consideration of undertaking a human trial in subjects according to this CTP the Sponsor will:

- indemnify the Investigator and hold him without liability for claims for damages arising out of the above described investigation in excess to those covered by his/her own professional liability insurance;
- defend the Investigator against any claims or lawsuits initiated by, or on behalf of, subjects who seek damages for bodily injury alleged to have been sustained as a result of administration of the study drug;
- pay any settlements of judgement resulting therefrom, providing that for all of the aforementioned cases, the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor;

Indemnification is not valid for claims for damages arising from malpractice and/or negligence on the part of the Investigator or those under the Investigator's supervision.

The protection afforded by this policy does not take the place of the Investigator's professional liability insurance but covers damages in excess of such insurance protection. Further, this indemnity is conditional upon the Investigator giving the Sponsor information as soon as reasonably practicable and upon the Investigator assisting the Sponsor and its authorised representatives in the investigation and defence of any suit for which coverage is provided.

26. CLINICAL TRIAL REPORT

A CTR of the trial will be prepared and written by the CRO according to ICH topic E3 (CPMP/ICH/137/95). A summary of the report will be sent to Investigators/EC/Regulatory Authorities according to current regulations.

27. USE OF INFORMATION AND PUBLICATION

Investigator agrees to inform in advance Zambon about his/her intention to divulge any data, results concerning the Confidential Information and/or the trial subject to this agreement. As a consequence hereof, Investigator hereby undertakes to submit to Zambon, at least with a 60 days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon's rights to preserve and protect its intellectual

property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the trial is conducted .

Further, without any prejudice to Investigator's right to divulge and save for what stated hereinabove, Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the trial hereto.

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29. APPENDICES

Appendix 1: Trial Flow Chart

Appendix 2: SmPC of NAC

Appendix 3: PI of ambroxol hydrochloride

Appendix 4: Investigator Signature Page

Appendix 1

Trial Flow Chart

ACTIVITIES (See sections 9 & 10 for details)	Visit 1 Screening	Visit 2 Randomisation		Visit 3			Visit 4 End of treatment (EoT)	Follow-up phone call or Visit	Unscheduled deterioration visit	Premature discotinuation visit)
	Within 7 days of Visit 2	Day 1	Day 2	Day 3	Day 4	Day 5 & 6	Day 7	2 weeks ± 3 days after EoT or DV		
Informed consent	X									
Verification of eligibility for randomization	X	X								
Medical history/demography	X									
Pregnancy test		X					X		x	X
Vital signs	X	X		X			X		x	X
Physical examination	X	X		X			X		x	X
Previous/concomitan medications	X	X		X			X	X		X
12-lead ECG	X						X		x	X
Blood sample for haematology and clinical chemistry	X						X			X
Assessment of expectoration difficulty, sputum viscosity, sputum colour and cough by means of the 4-point ordinal scales provided		x		x			x		X	X
24-h sputum collection (to be collected and measured the following day)		X		X			X			X
IMP dispensation		X	X	X	X	X	X			
Accountability of IMP		X	X	X	X	X	X		X	X

AE monitoring	X	X		X			X	X	x	X

Appendix 2
Summary of Product Characteristics – N-Acetyl cysteine (NAC)
Switzerland

Fluimucil 10%

Qualitative and quantitative composition

Active ingredient: Acetylcysteine.

Excipients: Sodium edetate, Aqua q.s. to solution.

Pharmaceutical form and quantity of active ingredient per unit

Injection solution for i.v., i.m., local application.

Ampoules: 300 mg acetylcysteine per 3 mL (100 mg/mL).

Therapeutic indications

In respiratory tract diseases that lead to the formation of viscous secretions, which can not be or can only be insufficiently expectorated

Pneumology: All forms of bronchitis, emphysema, atelectasis, bronchiectasis, cystic fibrosis.

ENT diseases: Laryngitis, sinusitis, pharyngitis and laryngectomised patients.

Surgery: Prophylaxis of bronchopulmonary complications with mucostasis.

Paediatrics: Bronchitis, cystic fibrosis.

Intoxications: Antidote for paracetamol intoxications.

Posology and method of administration

Inhalative application

Adults: inhale 1 ampoule 1-2 times a day.

Children of an age where they can actively participate: inhale ½ ampoule 1-2 times a day.

Instillations

Adults

Intraauricular and intranasal: 2-3 drops 2-3 times a day;

Endotracheal: 10-20 drops up to 1 ampoule 1-2 times a day;

Rinsing of other body cavities: ½ ampoule per rinse.

Children

Intraauricular and intranasal: 1-2 drops 1-2 times a day;

Endotracheal: 10 drops up to ½ ampoule 1-2 times a day.

Intravenous use

As a mucolytic in intensive care

Adults: 2-3 ampoules 2-3 times a day.

Children (see «Special dosage instructions»): 1-1½ ampoules 2-3 times a day.

It is recommended to dilute the ampoules with a 0.9% NaCl solution or with a 5% glucose solution and administer the solution slowly as a short infusion (over approx. 5 min.).

Intramuscular use

Adults: 1 ampoule 1-2 times daily by deep i.m. injection.

Children (see «Special dosage instructions»): ½ ampoule 1-2 times daily by deep i.m. injection.

Antidote for paracetamol intoxications

Intravenous dosage schedule according to Prescott

Total dosage: 300 mg/kg acetylcysteine, total duration 20 h.

The following treatment schedule is recommended:

Patients weighing ≥ 20 kg

For this specific use, the 20% concentration ampoules (Fluimucil 20%) are more suitable.

Patients weighing less than 20 kg:

Initial bolus 150 mg/kg in 3 mL/kg solution (over 60 min) followed by 50 mg/kg in 7 mL/kg (over 4 h), followed by 100 mg/kg in 14 mL/kg (over 16 h).

Depending on body weight, the 20% concentration ampoules (Fluimucil 20%) may be more suitable.

A faster initial bolus over 15 minutes may also be administered, but a slower bolus administration (over 60 minutes) reduces the likelihood of anaphylactoid reactions.

Special dosage instructions

Children: In infants and babies under 1 year of age, the product should only be administered under inpatient medical supervision.

In children under 6 years, oral treatment with appropriate dosage forms may be preferable to parenteral treatment.

Contraindications

Hypersensitivity to the active ingredient acetylcysteine or to any of the excipients mentioned in section *composition*.

Special warnings and precautions for use

Intravenous administration of acetylcysteine should be performed under strict medical supervision. Undesirable effects of treatment with acetylcysteine are more likely to occur if

administration is too rapid or excessive. It is therefore recommended that dosage instructions are strictly adhered to.

In patients weighing less than 40 kg, the (antidote)administration should be carefully dosed, because of the potential risk of hypervolemia (fluid overload) which may lead to hyponatremia and seizures. It is therefore recommended that dosage instructions are strictly adhered to.

In cases of direct intravenous administration of high doses (as antidote), pseudo-anaphylactic reactions have been observed occasionally.

For this reason, patients should be monitored and at the onset of the first symptoms, adequate therapeutic measures should be taken.

For aerosol treatment of asthma patients, it is advisable to administer Fluimucil 10% simultaneously with bronchodilators.

Simultaneous administration of an antitussive drug may, by suppressing the cough reflex and physiological self-cleaning of the respiratory tract, result in congestion of the mucus with risk of bronchospasm and respiratory tract infection.

Patients with bronchial asthma should be closely monitored during treatment. If a bronchospasm occurs, acetylcysteine must be discontinued and adequate therapeutic measures taken.

Caution is advised in patients with risk of gastrointestinal bleeding, especially during concomitant administration with other medicinal products inducing irritation of the gastric mucosa.

Administration of acetylcysteine may prolong prothrombin time in addition to paracetamol toxicity.

Information in case of low-sodium diet

Fluimucil 10% contains 43 mg sodium (1.9 mmol) per 3 ml ampoule.

Interactions

There are no *in vivo* interaction studies for the medication.

So far, the reports mentioning an inactivation of antibiotics by acetylcysteine relate exclusively to *in-vitro* studies in which the substances concerned had been directly mixed. Therefore, Fluimucil 10% should not be co-administered with other medicinal products in the same solution (see "Other Information, Incompatibilities").

Since thiol compounds may form addition compounds with naphthoquinones, there is also the theoretical possibility that a reaction with vitamin K may occur. Although it has not been

established whether this can occur *in vivo*, the administration of vitamin K for the treatment of hypoprothrombinemia in liver failure should begin a few hours after the cessation of acetylcysteine administration.

The vasodilatory and the inhibiting thrombocytes aggregation effects may be enhanced by the simultaneous administration of glyceryl trinitrate (nitroglycerin). The clinical importance of these findings has not yet been determined.

If co-treatment with parenteral nitroglycerin and acetylcysteine is considered necessary, the patient should be monitored for potential hypotension, which may be severe and may be indicated by the presence of headache.

Pregnancy/Breast-feeding

Pregnancy

Data from a limited number of exposed pregnant women showed no adverse effects on pregnancy or the health of the foetus or the newborn.

Experience from epidemiological studies is not available.

Animal studies have not indicated any direct or indirect toxicity with any effect on pregnancy, embryonic development, development of the foetus and/or postnatal development.

If used during pregnancy, caution is advised.

Breast-feeding

There are no studies showing whether or not acetylcysteine passes into breast milk.

Effects on ability to drive and use machines

Effects on the ability to drive or operate machinery has not been studied.

Undesirable effects

The most common undesirable effects described in the literature regarding the acetylcysteine administered intravenously are skin rash, urticaria and pruritus, and they most commonly occur during administration of the initial bolus.

In a randomised, open multi-centre study, during the first 2 hours after i.v. administration of acetylcysteine, the following undesirable effects occurred:

Immune system disorders

Very common: anaphylactoid reaction (17%).

Cardiac disorders

Common: Tachycardia.

Respiratory, thoracic and mediastinal disorders Uncommon: Pharyngitis, rhinorrhoea, rhoncus, bronchospasm.

Gastrointestinal disorders

Common: Vomiting (11%), nausea.

Skin and subcutaneous tissue disorders Common: Pruritus, skin rash.

Vascular disorders

Common: Facial flushing.

The following undesirable effects have been reported based on long-term post-marketing experience and their frequency can not be estimated from the available data.

Local administration

Immune system disorders: Hypersensitivity reaction.

Respiratory, thoracic and mediastinal disorders: Bronchospasm, rhinorrhoea.

Gastrointestinal disorders: Stomatitis, vomiting, nausea.

Skin and subcutaneous tissue disorders: Angioedema, urticaria, rash, itching.

Systemic administration (high dose i.v. administration)

Immune system disorders: Anaphylactic shock, anaphylactic/anaphylactoid reactions, hypersensitivity reaction.

Cardiac disorders: Tachycardia.

Respiratory, thoracic and mediastinal disorders: Bronchospasm, dyspnoea.

Gastrointestinal disorders: Vomiting, nausea.

Skin and subcutaneous tissue disorders: Angioedema, urticaria, facial flushing, rash, itching.

General disorders and administration site conditions: Face oedema.

Investigations: blood pressure decreased, prothrombin time prolonged.

The occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome has been very rarely reported in temporal relation to the use of acetylcysteine. In case of new manifestations of cutaneous and mucosal manifestations, a doctor should be consulted immediately and the use of acetylcysteine should be discontinued. In most of these reported cases, at least one other drug had been used and possibly enhanced the observed mucocutaneous effects.

Different studies confirm the decrease in Platelet aggregation when using acetylcysteine. The clinical significance of this is still unknown.

Overdose

Intravenous administration

Symptoms of overdose with intravenous administration are similar to adverse effects, but more pronounced.

In case of overdose, discontinue the infusion and initiate symptomatic treatment.

There is no specific antidote treatment. Acetylcysteine is dialysable.

Local administration

No cases of overdose have been reported with local administration.

Pharmacodynamic properties

ATC-code: R05CB01

Mechanism of action and pharmacodynamic properties

Fluimucil 10% contains the active ingredient acetylcysteine, a cysteine derivative with a free SH group that has both mucolytic and antioxidant properties.

The mucolytic effect of acetylcysteine relies on the ability of the SH group to reduce the disulphide bridges of the mucoproteins of the mucus.

The antioxidant property of Fluimucil 10% is based on the fact that electrophilic and oxidative compounds are directly inactivated by acetylcysteine and indirectly via glutathione. Electrophilic compounds are inactivated by conjugation, and oxidizing compounds are neutralized by reduction.

Acetylcysteine provides an essential precursor to glutathione synthesis through cysteine, increasing endogenous glutathione levels.

Glutathione is an important nucleophilic and antioxidant mechanism of action of the organism and is therefore of great importance for its protection. Glutathione may also inactivate the toxic, reactive, electrophilic metabolites produced in certain intoxications (e.g., paracetamol intoxication) by forming inert complexes.

Fluimucil 10% does not affect the body's immune defenses nor the ciliary function of the respiratory tract and does not cause dissolution of fibrin or blood clots.

Clinical efficacy

Fluimucil 10% dissolves the viscous mucus in the airways, promotes expectoration and helps allay the coughing stimulus. This facilitates breathing.

Other clinical parameters that may be positively influenced by Fluimucil 10% include dyspnoea and lung function.

When used as an antidote for paracetamol intoxications, Fluimucil 10% works by restoring the glutathione level in hepatocytes or, in its place, as an alternative substrate promoting the conjugation of toxic metabolites of paracetamol.

Pharmacokinetic properties

Following i.v. administration, acetylcysteine diffuses rapidly in the body, mainly in the aqueous medium of the extracellular space and reaches the highest concentrations in the liver, kidneys, lungs and bronchial mucus.

In the body, acetylcysteine is found either in free form or reversibly plasma protein bound by disulfide bridges.

Following i.v. dosage of 200 mg of acetylcysteine the following pharmacokinetic data was obtained.

The maximum plasma concentration of total acetylcysteine (free and bound) was 120 µmol/L, for the free form it was 75 µmol/l.

The volume of distribution was 0.47 L/kg (free and bound), or 0.59 L/kg (free form). Total clearance was determined as 0.11 L/h/kg (total) and 0.84 L/h/kg (free). Elimination half-life was approx. 5.6 h, and for the free form approx. 2 h.

In newborns or patients with severe hepatic insufficiency, a prolonged elimination half-life is to be expected.

Elimination

About 30% of the administered dose is eliminated directly by the kidneys. The main metabolites are cystine and cysteine. In addition, small amounts of taurine and sulphates are excreted.

No studies are available on the excretion of the portion not eliminated through the kidneys.

Preclinical safety data

Mutagenic effects of acetylcysteine are not expected. A test on bacterial organisms was negative. Studies on the tumorigenic potential of acetylcysteine were not carried out.

Embryotoxicity studies have been conducted in pregnant rabbits and rats, to which a dose of oral acetylcysteine has been administered during the gestation period. None of these experimental studies revealed fetal malformations. Fertility, peri- and postnatal development studies were performed in rats with oral acetylcysteine. The results of these studies demonstrate that acetylcysteine does not affect gonadal function, fertility, infants, or the development of newborn animals.

Other information

Incompatibilities

Acetylcysteine is incompatible with most metals and is inactivated by oxidising substances. Therefore, if possible, containers made of glass or plastic (but not rubber) should be used for administration.

Fluimucil 10% should not be co-administered with other medicinal products, in particular antibiotics, in a single solution or within the same container.

Influence on diagnostic methods

Acetylcysteine may affect the colourimetric assay of salicylates.

In urinalysis, acetylcysteine may affect the results when determining ketone bodies.

Shelf life

Unopened ampoules may not be used after the date stated on the container after "Exp".

If the ampoule has been opened, discard any unused solution.

Special precautions for storage

Store at room temperature (15-25 °C) in the original packaging, in order to protect from light, and keep out of the sight and reach of children.

Instructions for use

Instruction for opening the ampoule

- Keep the ampoule in the correct position (i.e., with the marked point upwards) (Figure 1)
- Apply pressure with the thumb above the point and break the ampoule head away (Figure 2)

I.V. administration

Fluimucil 10% is compatible with the following solutions for infusion: 5% glucose solution and 0.9% NaCl solution. The diluted infusion preparation is not preserved. It is chemically and physically stable for 24 hours at room temperature.

However, for microbiological reasons, the ready-to-use preparation should be used immediately after dilution. Any remaining solution must be discarded.

Aerosol therapy

For aerosol use, administration should be performed using an inhalation device. Dilution of the ampoule is not necessary, yet is possible (e.g., 1 ampoule of Fluimucil 10% (3 mL) + 7 mL of 0.9% NaCl solution to reach a final volume of 10 mL).

The use of equipment with glass or plastic parts is preferable.

If equipment with metal or rubber parts is used, rinse immediately with water after use.

Marketing authorisation number

66860 (Swissmedic).

Packaging

Fluimucil 10% solution for injection ampoule 5 × 3 mL. (B)

Marketing authorisation holder

Zambon Switzerland AG, 6814 Cadempino.

Date of information

May 2012

Appendix 3
Package Insert – Ambroxol hydrochloride
China

[Drug Name]

Generic name: Ambroxal Hydrochloride Injection

English name: Ambroxal Hydrochloride Injection

Trade name: Mucosolvan

[Composition]

Ambroxol hydrochloride (also known as bromocyclohexylaminealcohol hydrochloride)

Excipients: Citric acid monohydrate, sodium hydrogen phosphate dihydrate, sodium chloride, water for injection, nitrogen.

[Description]

Colorless clear liquid.

[Indication]

1. Indicated for expectorant therapy in the following patients with acute and chronic respiratory diseases accompanied by abnormal sputum secretion and poor expectoration, such as acute exacerbation of chronic bronchitis, asthmatic bronchitis, bronchiectasis, bronchial asthma and pneumonia.
2. Prophylactic treatment of postoperative pulmonary complications.
3. Treatment of infant respiratory distress syndrome (IRDS) in premature infants and newborns.

[Dosage and Administration]

Adults and children above the age of 12 years: 2-3 times a day, 15 mg each time, slow intravenous injection; the dose can be increased to 30 mg each time for severe cases.

Children aged 6-12 years: 2-3 times a day, 15 mg each time.

Children aged 2-6 years: 3 times a day, 7.5 mg each time.

Children below the age of 2 years: 2 times a day, 7.5 mg each time.

All for slow intravenous injection.

Or add the drug to glucose injection (or normal saline) for intravenous drip.

Treatment of infant respiratory distress syndrome (IRDS): The total daily dose is calculated based on the infant's weight, 30 mg/kg, divided into 4 injections per day. An infusomat should be used for administration, and the duration of intravenous injection should be at least 5 minutes.

[Dosage Form]

Injection

[Adverse Reactions]

The product is well tolerated, and mild upper gastrointestinal adverse reactions have been occasionally reported, mainly including stomach burning, indigestion and occasional nausea and vomiting, occurring mostly after parenteral administration. Allergic reactions are rare, mainly including rash. Few cases have reported severe acute allergic reactions, but the correlation with ambroxol hydrochloride is not yet known, and such patients are often allergic to other substances.

[Contraindication]

Those who are known to be allergic to ambroxol hydrochloride or other ingredients shall not use the product.

[Precautions]

1. Pregnant and breastfeeding women should use the product with caution.

2. It is prohibited to mix the product with other solutions having a pH greater than 6.3, as the increase in pH will lead to free base precipitation of ambroxol.

[Ingredient]

Ambroxol hydrochloride

[**Use in Pregnant and Breastfeeding Women**]

Pre-clinical trials and a great deal of clinical experience in women after pregnancy for 28 weeks have shown that the product has no adverse effect on pregnancy. However, during pregnancy, especially in the first three months of pregnancy, the drug should be used with caution. The drug may enter breast milk, but is supposed to have no effect on infants at the therapeutic dose.

[Pediatric Use]

Keep observing during medication.

[Geriatric Use]

The safety and efficacy of medication in the elderly and young patients have been assessed, and the results have shown no difference.

[Drug Interactions]

Co-administration of the product and antibiotics (amoxicillin, cefuroxime, erythromycin, doxycycline) may increase the concentration of antibiotics in the lung tissue. There has been no report on relevant clinical adverse reactions when the product is used in combination with other drugs.

[Pharmacological Action]

The product is a mucolytic agent, which can increase respiratory mucosal serous gland secretion, and reduce mucus gland secretion, thereby reducing the viscosity of sputum; it can also promote the secretion of pulmonary surfactants, and increase bronchial cilia movement, so that sputum can easily be coughed up.

[Manufacturer]
Boehringer Ingelheim Shanghai Pharmaceutical Co., Ltd.

Appendix 3: Investigator Signature Page

I have read the attached protocol: **Intravenous NAC Phase III China Trial.** A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with abnormal sputum viscosity and poor expectoration

I agree to comply with the current International Council for Harmonisation Guidelines for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved.

I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred or if any proceeding for debarment is pending or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the EC.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

PPD

(Printed Name)

PAREXEL International
NOTE TO FILE

SPONSOR: Zambon S.p.A	**PAREXEL PROJECT NUMBER:** CCI
SPONSOR PROTOCOL NUMBER: Z7244L01	**TEST MATERIAL: NAC**
INVESTIGATOR NAME/ADDRESS: NA	**SITE NUMBER:** NA

SUBJECT: Clarification of footer and the numbering of the Appendix Section of Leading PI signature page

This document is to clarify footer and heading discrepancy on PI Signature Page for Final Protocol v1.0.

The protocol version 1.0 dated 29 Aug 2018 was released to Parexel on 30 Aug 2018, and Qualification Visit of the leading site occurred on the 11 Sep 2018 and at that time the signature of the leading Principal investigator was obtained on the protocol version 1.0 dated 29 Aug 2018

Following discrepancies were noted later and notified to Zambon on the 23 Oct 2018

1. The Final Protocol page 53 onwards (for Appendix 2 onwards) footer indicated Draft V2 (27 Mar 2018) SOP C03.02.06 App.1.

2. Although the Protocol listed PI Signatures under Appendix 4 (Section 29 of Protocol), inadvertently on the signature page it was a typo error of Appendix 3.

The protocol was corrected to have version 1.0 dated 29 Aug 2018 as footer on all pages and sent to Parexel on 23 Oct 2018. The Appendix was also updated from Appendix 3 to 4 for the PI signature page. There were only changes in the format of this protocol.

Since the signature page of leading principal investigator for protocol version 1.0 were obtained before the 23 Oct 2018, no new signature pages were retrieved from leading principal investigator. Therefore, on the PI Signature age for Protocol v1.0, Heading is Appendix 3 and footer has version as draft V2 (27Mar2018)"

China regulatory authority comments were anticipated to be released in Dec 2018 with changes in the protocol version thereafter.

A new protocol version 2.0 dated 19 Dec 2018 was released for the study. Leading Principal investigator signature for the protocol version 2.0 dated 19 Dec 2018 was obtained.

This document has been signed electronically or on the final page by the following:

Date	Signatory
	PPD

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: PPD
Title: PPD
Date: Tuesday, 15 June 2021, 03:31 AM GMT Standard Time
Meaning: Document contents approved.
==========

PROTOCOL AMENDMENT

NUMBER: 1

INTRAVENOUS NAC PHASE III CHINA CLINICAL TRIAL
(IVNAC-3C)

A PHASE III, MULTI-CENTRE, RANDOMIZED, RATER- AND PATIENT-BLIND, PLACEBO- AND ACTIVE-CONTROLLED, PARALLEL GROUP CLINICAL TRIAL TO COMPARE THE EFFICACY AND SAFETY OF 1-WEEK TREATMENT WITH INTRAVENOUS N-ACETYLCYSTEINE (NAC) 600 MG TWICE DAILY (ACTIVE TEST TREATMENT), AMBROXOL HYDROCHLORIDE 30 MG TWICE DAILY (ACTIVE CONTROL TREATMENT) AND PLACEBO AS EXPECTORANT THERAPIES IN ADULT CHINESE PATIENTS WITH RESPIRATORY TRACT DISEASES AND ABNORMAL MUCUS SECRETIONS

Protocol Code
Z7244L01

DATE OF THE AMENDMENT: 19 December 2018

Zambon Spa
Via Lillo del Duca 10
20091 Bresso - Milan - Italy

Clinical Trial Title: Intravenous NAC Phase III China Trial

A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with respiratory tract diseases and abnormal mucus secretions

APPROVALS:

As agreed and approved:

	PPD	
Date (d,m,y)	**Global Chief Medical Officer**	**SIGNATURE**
	PPD	
Date (d,m,y)	**Global Medical Affairs Head** **Established & Respiratory Medicines**	**SIGNATURE**

PROTOCOL AMENDMENT n.1

This amendment is considered not substantial because the introduced changes do not impact the subject's safety and efficacy or quality of the investigational drug. In detail:

Protocol section	**Text of the protocol version 1.0**	**Amended text of the protocol version 2.0**	**Rational for the change**
4. INTRODUCTION AND RATIONALE	This trial is intended to provide pivotal (phase III) evidence of efficacy and safety for registration in China of slow intravenous infusion of NAC in adult hospitalised patients with with respiratory tract diseases and abnormal mucus secretions.	This trial is intended to provide pivotal (phase III) evidence of efficacy and safety for registration in China of slow intravenous infusion of NAC in adult hospitalised patients with respiratory tract diseases and abnormal mucus secretions.	Typing error
Exclusion criteria number 4	Use of expectorants or drugs with expectorant effect within 3 days before randomization visit	Use of expectorants or drugs with expectorant effect within 2 days before randomization visit	A period of 48 hours is sufficient to ensure the washout from expectorants or drugs with expectorant effect and to ensure the validity of efficacy assessment.
8.1. CLINICAL TRIAL DESIGN	The trial will be conducted in approximately 15 -25 sites in China.	The trial will be conducted in approximately 25 sites in China.	Administrative change
8.1. CLINICAL TRIAL DESIGN	The study will consist of a total of 4 core hospital visits (screening, baseline, treatment day 3, treatment day 7, see Section 9)	The study will consist of a total of 4 core hospital visits (screening, baseline, treatment day 3, treatment day 7, see Section 10)	Typing error
8.2. DURATION OF CLINICAL TRIAL	If the trial is prematurely stopped, please refer to Section 16	If the trial is prematurely stopped, please refer to Section 17	Typing error

9.2.1. INCLUSION CRITERIA	1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as: acute bronchitis, chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis	1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as: acute bronchitis, chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis. Diagnostic criteria for these conditions are provided in Annex 1	Added following an NMPA suggestion
9.2.1. INCLUSION CRITERIA	1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as: acute bronchitis, chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis.Chinese ethnicity and/or Chinese	2. Chinese ethnicity and/or Chinese	Typing error
9.2.2. EXCLUSION CRITERIA		5. Diagnosis of active tuberculosis, lung cancer, pulmonary fibrosis, acute pulmonary thromboembolism or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the patient or affect the interpretation of the results	Added following an NMPA suggestion
9.2. SELECTION OF SUBJECTS	Although teratology studies carried out in	Although teratology studies carried out in	Administrative change

Contraceptive methods	animals evidenced no teratogenic effects of NAC (ref IB) or ambroxol hydrochloride (ref SmPC Italy), safety in human pregnancy has not been established with iv administration.	animals evidenced no teratogenic effects of NAC (ref IB) or ambroxol hydrochloride (ref Package Insert China), safety in human pregnancy has not been established with iv administration.	
Several sections	sputum colour	sputum color	Typing error
11.1.6	Abnormalities of clinical significance recorded at V1, Visit 4 or unscheduled deterioration visit/premature discontinuation visit which are not related to pre-exist medical condition before ICF signature will be reported as AEs.	Abnormalities of clinical significance recorded at Visit 1, Visit 4 or unscheduled deterioration visit/premature discontinuation visit which are not related to pre-exist medical condition before ICF signature will be reported as AEs.	Typing error
12. PRIOR AND CONCOMITANT TREATMENTS	• Appropriate treatment(s) for any underlying disease, that in the investigator's opinion will not interfere with the measurements contributing to the primary efficacy outcomes. If one or more treatments interfering with the measurements contributing to the primary efficacy outcomes are deemed necessary, the patient should not be randomized or should be discontinued from the study.	• Appropriate treatment(s) for any respiratory tract disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes, such as: corticosteroids (inhaled or systemic), bronchodilators, antibiotics (in case of co-administration, the i.v. antibiotic should be administered separately). • Appropriate treatment(s) for any other underlying disease, that in the investigator's opinion	Administrative change (the section has been aligned to the synopsis)

		will not interfere with the measurements contributing to the efficacy outcomes • If co-treatment with parenteral nitroglycerin is needed the patients should be monitored for potential hypotension, which may be severe and may be indicated by the presence of headache • If one or more treatments interfering with the measurements contributing to the primary efficacy outcomes are deemed necessary, the patient should not be randomized or should be discontinued from the study All concomitant medications will be recorded and analysed as described in Section 20.4.3.3.	
13.1. INVESTIGATIONAL MEDICINAL PRODUCT SUPPLIES AND PACKAGING	NAC will be supplied in boxes containing 2 ampoules each.	NAC will be supplied in boxes containing 4 ampoules each.	Administrative change
13.1. INVESTIGATIONAL MEDICINAL PRODUCT SUPPLIES AND PACKAGING	Ambroxol hydrochloride will be supplied in boxes containing 2 vials each.	Ambroxol hydrochloride will be supplied in boxes containing 4 vials each.	Administrative change
13.1.	Placebo will be	Placebo will be	Administrative

INVESTIGATIONAL MEDICINAL PRODUCT SUPPLIES AND PACKAGING	supplied in boxes containing 1 vial each.	supplied in boxes containing 2 vials each.	change
13.2. INVESTIGATIONAL MEDICINAL PRODUCT DISPENSING AND ADMINISTRATION	All IMPs will be administered at the hospital investigational sites by study staff otherwise not involved with the assessment and care of study patients. The study staff members administering the IMP will be aware of its identity but will not disclose it to patients or to other study staff members (patient and rater-blind design, see Section 4).	All IMPs will be dispensed twice daily as one in the morning and another is in the afternoon/evening for a week of treatment period at hospital investigational sites by study staff. All IMP will be administered at the hospital investigational sites by study staff otherwise not involved with the efficacy assessment and care of study patients. The study staff members administering the IMP will be aware of its identity but will not disclose it to patients or to other study staff members who are involved in efficacy assessment (patient and rater-blind design, see Section 4).	To further guide the IMP dispensing and administration procedure.
13.3. RANDOMISATION	The screening number will consist of country number (3 digits), a site number (3 digits) and a continuous number for a subject at an individual site (3 digits), e.g. 001001001. Every subject who signs the ICF must be entered	The screening number will consist of country number (1 digit), a site number (3 digits) and a continuous number for a subject at an individual site (3 digits), e.g. 1001-001. Every subject who signs the ICF	Administrative change

	into the IWRS system regardless of eligibility.	must be entered into the IWRS system regardless of eligibility.	
18.3.2. DEFINITION OF MEDICAL DEVICE MALFUNCTION AND INCIDENT	A medical device malfunction is the failure of a device to meet performance specifications or to perform as intended. A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, a user, or other persons, or to a serious deterioration in their state of health. A medical device complaint meeting the criteria of a potential medical device incident is reportable. Subjects will also be monitored for any medical device malfunction or incident and, if these occur, details will be recorded as for ADRs.		Not applicable section, therefore has been removed
18.4.1. DEFINITION OF SERIOUS ADVERSE EVENT OR SERIOUS ADVERSE REACTION	A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is any untoward medical occurrence or effect that at any dose:	A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:	Typing error
18.4.1. DEFINITION OF SERIOUS ADVERSE EVENT	• requires inpatient hospitalisation or prolongation of existing	• requires inpatient hospitalisation or prolongation of	Administrative change (hospitalization

OR SERIOUS ADVERSE REACTION	hospitalisation;	existing hospitalisation considering that hospitalization is not a SAE in itself, planned or selective hospitalization, hospitalization for underlying disease which did not worsen during the study, as well as hospitalizations for social reasons should not be reported as SAEs;	definition added)
18.7. ADVERSE EVENT RECORDING	The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF.	The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF and on the "Serious Adverse Event Form" (if appropriate).	Administrative change
18.9.1. REPORTING SERIOUS ADVERSE EVENTS	The back-up procedure is to send the back-up paper Serious Adverse Event Form to the CRO's Pharmacovigilance group by email or fax using the contact details specified in the SAE guidelines.	The back-up procedure is to send the back-up paper Serious Adverse Event Form to the CRO's Pharmacovigilance group by email using the contact details specified in the SAE guidelines.	Administrative change (fax deleted)
18.9.1. REPORTING SERIOUS ADVERSE EVENTS	If the Investigator becomes aware of any SAE outside the follow-up window established in this CTP, it is the Investigator's responsibility to report the SAE to the CRO. The Investigator might	If the Investigator becomes aware of any SAE is related to the study drug outside the follow-up window established in this CTP, it is the Investigator's responsibility to	Administrative change

	use the eCRF, as described above. However, the SAE is not an event occurred within the trial period.	report the SAE to the Sponsor. The Investigator might use the "Serious Adverse Event Form" via email, but the SAE must not to be reported in the CRF, the SAE is not an event occurred within the trial period.	
18.10. FOLLOW-UP FOR ADVERSE EVENTS	All AEs requiring the subject's discontinuation and SAEs will be followed up until they are resolved or closed.	All AEs requiring the subject's discontinuation and SAEs will be followed up until they are resolved or closed or when the subject is lost to follow up or uncontactable.	Administrative change
18.10. FOLLOW-UP FOR ADVERSE EVENTS	If follow-up information on SAEs is available, a follow-up eCRF form will be filled-in by the Investigator and sent to the CRO as above-described, under Section 18.8.1.	If follow-up information on SAEs is available, a follow-up information will be filled-in eCRF by the Investigator and sent to the CRO as above-described, under Section 18.9.1.	Administrative change
18.11. PREGNANCY	In the event that a subject or a female partner is found to be pregnant after inclusion in the trial, then pregnancy will be actively followed up to term and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the CRO. The Investigator will send pregnancy	In the event that a subject or a female partner is found to be pregnant after inclusion in the trial, then pregnancy will be actively followed up to term or pregnancy termination and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the	Administrative change

	reports within the timeframes of SAEs. If pregnancy results in abnormal outcome, the Investigator and/or the Sponsor considers this to be due to the IMP, will be treated as an expedited ADR report.	CRO. The Investigator will send pregnancy reports using pregnancy Reporting and Outcome form to CRO within the timeframes of SAEs. If pregnancy results in abnormal outcome, it will be considered as SAE. If the Investigator and/or the Sponsor considers this to be due to the IMP, this will be treated as an expedited ADR report.	
20.4.3.1. ANALYSIS OF PRIMARY END-POINTS	Statistical significant results will be needed on both mITT and PP populations to accept the hypothesis of non-inferiority of NAC versus ambroxol.	Statistically significant results will be needed on both mITT and PP populations to accept the hypothesis of non-inferiority of NAC versus ambroxol.	Typing error
20.4.3.1. ANALYSIS OF PRIMARY END-POINTS	The co-primary efficacy endpoints are: “the change from baseline to the 1-week treatment in sputum viscosity score” and “the change from baseline to the 1-week treatment in expectoration difficulty score” and will be analyzed on the mITT and PP populations by means of conventional Mann-Whitney U Statistics for testing the hypotheses of superiority of NAC versus placebo (primary objective))	The co-primary efficacy endpoints are: “the change from baseline to the 1-week treatment in sputum viscosity score” and “the change from baseline to the 1-week treatment in expectoration difficulty score” and will be analyzed on the mITT and PP populations by means of stratified Mann-Whitney U Statistics for testing the hypotheses of superiority of NAC	Added following an NMPA suggestion

	and by means of a modified Mann-Whitney U Statistics [23]	versus placebo (primary objective) after blocking for baseline score and by means of a modified Mann-Whitney U Statistics [23]	
20.4.3.2. ANALYSIS OF SECONDARY ENDPOINTS	(Mann-Whitney U Statistics)	(stratified Mann-Whitney U Statistics blocking for baseline score)	Added following an NMPA suggestion
20.4.3.3. SUBGROUP ANALYSES		Upon completion of the study, the study statistician in consultation with Zambon's Clinical Team will determine the proportion of concomitant medications between the treatment groups and will decide whether to perform subgroup efficacy analyses if deemed appropriate. The analyses described for the primary and secondary efficacy endpoints will be performed separately for each of the identified stratums.	Added following an NMPA suggestion
22. ETHICS COMMITTEE APPROVAL	This trial will be undertaken only after written and dated approval from EC has been received by the Investigator and by the Sponsor for CTP, all its appendices, ICF, and subjects recruitment procedures (i.e. advertisement) if applicable.	This trial will be undertaken only after written and dated approval from EC has been received by the Investigator and by the Sponsor for CTP, all its appendices, ICF, and subject's recruitment procedures (i.e. advertisement) if applicable.	Typing error
29. ANNEX		Annex 1: Diagnostic	Added following an

		criteria for the underlying respiratory disease at baseline	NMPA suggestion
Annex 1		Diagnostic criteria for the underlying respiratory disease at baseline table and references	Added following an NMPA suggestion
Appendix 1	Premature discotinuation visit	Premature discontinuation visit	Typing error

CLINICAL TRIAL PROTOCOL

INTRAVENOUS NAC PHASE III CHINA CLINICAL TRIAL (IVNAC-3C)

A PHASE III, MULTI-CENTRE, RANDOMIZED, RATER- AND PATIENT-BLIND, PLACEBO- AND ACTIVE-CONTROLLED, PARALLEL GROUP CLINICAL TRIAL TO COMPARE THE EFFICACY AND SAFETY OF 1-WEEK TREATMENT WITH INTRAVENOUS N-ACETYLCYSTEINE (NAC) 600 MG TWICE DAILY (ACTIVE TEST TREATMENT), AMBROXOL HYDROCHLORIDE 30 MG TWICE DAILY (ACTIVE CONTROL TREATMENT) AND PLACEBO AS EXPECTORANT THERAPIES IN ADULT CHINESE PATIENTS WITH RESPIRATORY TRACT DISEASES AND ABNORMAL MUCUS SECRETIONS

Protocol Code
Z7244L01

Protocol Name
IVNAC-3C (**I**ntra**V**enous **NAC** – Phase **3** **C**hina Trial)

Final Date: 19 December 2018

Version: Version 2.0

Zambon SpA
Via Lillo del Duca 10
20091 Bresso - Milan – Italy

APPROVAL PAGE

Protocol Title: Intravenous NAC Phase III China Trial

A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with respiratory tract diseases and abnormal mucus secretions

Protocol Name: IVNAC-3C (IntraVenous **NAC** – Phase **3 C**hina Trial)

Protocol Code: Z7244L01

Protocol Version and Date: Version 2.0 19 December 2018

Authors: PPD ,

Sponsor Name and Address: Zambon S.p.A.
Via Lillo del Duca 10
20091 Bresso - Milan – Italy

As agreed and approved:

PPD		
Date (dd/mm/YYYY)	**Global Chief Medical Officer**	**SIGNATURE**
PPD		
Date (dd/mm/YYYY)	**Global Medical Affairs Head Established & Respiratory Medicines**	**SIGNATURE**
____/____/____	_____	_____
Date (dd/mm/YYYY)	**Principal Investigator**	**SIGNATURE**

ZAMBON CONTACT DETAILS

Zambon S.p.A
Via Lillo del Duca 10
20091 Bresso - Milan (Italy)
Phone: PPD
Email PPD

Role	Name	Contact Data
Global Medical Affairs Head Established & Respiratory Medicines	PPD, MD, PhD	Phone: PPD PPD
Global Chief Medical Officer	PPD, MD	Phone: PPD PPD
Clinical Project Manager	PPD, PhD	Phone: PPD PPD
Global Head of Drug Safety - Pharmacovigilance contact	PPD, MD	PPD Phone: PPD
Statistician	PPD	PPD Phone: PPD

CONTRACT RESEARCH ORGANISATION CONTACT DETAILS

PAREXEL

Role	Name	Contact Data
Medical Monitor	PPD	PPD Phone: PPD
Contact for serious adverse event/pregnancy reporting	Safety Services Project Leader	PPD

OTHER INSTITUTIONS

Role	Name	Contact Data
Interactive Web Response System (IWRS)	PPD	PPD
Electronic Data Capture	PPD	PPD Phone: PPD

Role	Name	Contact Data
Investigational Medicinal Product (IMP) Packaging and Labelling;	PPD	PPD Phone: PPD
Investigational Medicinal Product (IMP) Logistic	PPD	PPD Phone: PPD

LIST OF COMMITTEES

Not applicable.

SUMMARY OF CHANGES HISTORY

Protocol Version	Key Changes
Protocol Version: Final 1.0	Original Protocol
Protocol Version: Final 2.0	No substantial changes

1. TABLE OF CONTENTS

2. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AH	Ambroxol hydrochloride
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CA	Competent Authority
C-FDA	Chinese Food and Drug Administration
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DV	Deterioration Visit
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EM	Expectation-Maximization
EMA	European Medicines Agency
EoT	End of Treatment
EU	European Union
GCP	Good Clinical Practice
γGT	gamma glutamyl transferase
GSH	Glutathione
HOCl	Hypochorous acid
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ITT	Intention-to-treat
IV	Intravenous
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive Web Response System
Kg	Kilograms
LOCF	Last Observation Carried Forward
MC	Monte Carlo
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mITT	Modified Intention to Treat
ml	Milliliter
MVTF	Missing Value Treatment Failure

NAC	N-acetylcysteine
NaCl	Sodium chloride
PI	Package Insert
PP	Per-protocol population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCM	Traditional Chinese Medicine
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
US-FDA	United States Food and Drug Administration
WHO-DD	World Health Organization-drug dictionary
WOCF	Worst Observation Carried Forward

3. SUMMARY

Title:	**Intravenous NAC Phase III China Trial** A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with respiratory tract diseases and abnormal mucus secretions
Protocol Code/	Z7244L01
Protocol Name:	**IVNAC-3C** (**I**ntra**V**enous **NAC** – Phase **3 C**hina Trial)
Phase:	III
Treatments	**Active test treatment** Ampoule containing 300 mg N-acetylcysteine (NAC) in 3 ml (Zambon Spa, Vicenza, Italy). Two ampoules (NAC 600 mg) in 10 ml NaCl 0.9% saline solution, administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 hours apart for 1 week (7 days). Total daily NAC dose: 1200 mg/day. **Active control treatment** Vial containing 15 mg Ambroxol Hydrochloride (AH) in 2 ml (Boehringer Ingelheim, Shanghai, China***).*** Two vials (AH 30 mg) in 10 ml NaCl 0.9% saline solution administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 hours apart for 1 week (7 days). Total daily AH dose: 60 mg. **Placebo treatment** Vial containing 10ml NaCl 0.9% saline solution (China Otsuka Pharmaceutical Co., Ltd.) One vial of 10 ml NaCl 0.9% saline solution administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 hours apart for 1 week (7 days).

Objectives:

Efficacy objectives

Primary objective

Demonstrate that slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score in adult Chinese hospitalized patients with respiratory tract diseases and abnormal mucus secretions

Secondary objectives

Efficacy objectives

Demonstrate in the same patient population that:

- slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to day 3 and end of 1-week treatment of other indicators of mucolytic activity (individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume);
- slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is non-inferior to slow intravenous infusion of ambroxol hydrochloride 30 mg twice daily in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score;
- slow (at least 5 minutes) intravenous infusion of ambroxol hydrochloride 30 mg twice daily is superior to placebo in change from baseline to day 3 and to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score and of other indicators of mucolytic activity: individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume.

Safety objectives

- Confirm that 1-week treatment with iv NAC 600 mg twice daily is safe and well tolerated.

Design:

Multicenter, randomized, rater- and patient-blind, placebo- and active-controlled, 3-arm parallel group clinical trial.

Subjects will be randomized to NAC or ambroxol or placebo in a 1:1:1 ratio.

The study will consist of a total of 4 core hospital visits and a follow-up call 2 weeks after end of treatment. If the patient is still hospitalized or if more convenient for the patient, the follow-up phone call can be replaced by a follow-up hospital visit.

Number of patients:	A total of 333 patients will be randomized. This number includes 10% overage to allow for patients who discontinue the trial prematurely ("drop-outs") without contributing to the primary end-point.
Trial duration:	Approximately 8 months. The enrolment period will be approximately 7 months.
Duration of patient participation:	Up to 4 weeks. Each patient will undergo a screening period of up to 1 week, a 1-week treatment period and a 2-week follow-up period.
Participating Countries:	China
Number of Sites:	Approximately 25
Population:	**Inclusion criteria** Patients will be enrolled in the trial if all of the following criteria are met: 1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as: acute bronchitis, chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis. Diagnostic criteria for these conditions are provided in Annex 1 2. Chinese ethnicity and/or Chinese 3. Signed the informed consent form before any study-related procedure 4. Sputum viscosity score ≥ 2 at randomization visit 5. Expectoration difficulty score ≥ 2 at randomization visit 6. Willingness and ability to comply with study procedures **Exclusion criteria** Patients will not be enrolled if one or more of the following criteria are met: 1. Intolerance or contra-indication to treatment with NAC or ambroxol or allergy to any component of the study treatments 2. (For female patients) ongoing pregnancy or lactation, or childbearing potential but unwillingness to adopt abstinence or contraception measures during the study 3. Intake of an investigational drug within 1 month before the screening visit 4. Use of expectorants or drugs with expectorant effect within 2 days before randomization visit

5. Diagnosis of active tuberculosis, lung cancer, pulmonary fibrosis, acute pulmonary thromboembolism or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the patient or affect the interpretation of the results
6. Medical history of and/or illness (including laboratory abnormality) and/or treatment that in the investigator's opinion may interfere with the patient's safety, compliance, or study evaluations
7. Serum ALT and/or AST more than 3 times above the upper limit of normal at screening visit
8. Serum creatinine more than 3 times above the upper limit of normal at screening visit
9. Addiction to alcohol or drugs
10. Mental illness, or other reasons for non-cooperation in the investigator's opinion

Outcome measures:

Efficacy variables

- Sputum viscosity, expectoration difficulty, sputum color and cough are assessed by means of ordinal categorical 4-point scales with 0 = best and 3= worst.
  For each patient the assessment is to be carried out by the blinded rater on treatment days 1 (baseline), 3 and 7 in the morning between 7 am and 9 am before administration of study drug. Should a patient discontinue prematurely from the trial (including discharge from the hospital before day 7) an assessment should be conducted on the day of discharge whenever possible.
  Scoring criteria are as follows:

	0	1	2	3
Sputum viscosity	Liquid (normal viscosity)	Fluid (mildly increased viscosity)	Viscous (moderately increased viscosity)	Sticky (severely increased viscosity)
Expectoration difficulty	No difficulty	Mild difficulty	Moderate difficulty	Marked difficulty
Sputum Color	Mostly white	Mostly pale yellow	Mostly dark yellow	Very dark yellow /green
Cough	No cough	Sporadic and mild cough	Moderate cough	Severe Cough

Adapted from [12].

- Sputum volume: patients will collect 24-hour sputum (morning to same time of the following morning) in a

graduated cup on treatment days 1 (Baseline), 3 and 7. Volume will be expressed as mL/24h.

Safety variables

- Adverse events assessed for severity and seriousness.
- Laboratory measurements including hematology, liver enzymes, serum creatinine.
- 12-lead electrocardiogram

End-points:

Primary efficacy end-point

Superiority of NAC over placebo in change from baseline to end of 1-week treatment of mean sputum viscosity score or mean expectoration difficulty score.

The study will be declared success if at least one of two components of the primary end-point will show superiority over placebo.

Secondary efficacy end-points

A. Superiority of NAC over placebo:

- in change from baseline to day 3 of mean sputum viscosity score OR mean expectoration difficulty score;
- in change from baseline to day 3 and to end of 1-week treatment of individual scores:
  - mean sputum viscosity score
  - mean expectoration difficulty score
  - mean sputum color score
  - mean cough score
- in change from baseline to day 3 and to end of 1-week treatment of mean sputum volume

B. Non-inferiority of NAC vs. ambroxol in change from baseline to end of 1-week treatment of mean sputum viscosity score or change of mean expectoration difficulty score.

C. Superiority of ambroxol vs. placebo in change from baseline to day 3 and to end of 1-week treatment of
   - mean sputum viscosity score OR mean expectoration difficulty score;
   - mean sputum viscosity score (individual score)
   - mean expectoration difficulty score (individual score)
   - mean sputum color score
   - mean cough score
   - mean sputum volume

Safety end-points

Counts and frequency distributions of

- all, mild/moderate/severe, non-serious/serious adverse events
- vital signs
- Laboratory tests

- 12-lead ECG (normal, abnormal clinically non- significant, abnormal clinically significant)

Statistical Analysis:

Sample size justification

This study has been powered to reach statistical significance for the superiority comparisons of N-acetyl-cysteine (NAC) vs. placebo (primary study objective), and for the non-inferiority comparisons of NAC vs. ambroxol hydrochloride (secondary study objective) in at least one of the two co-primary endpoints at the end of the 1-week treatment. To control the overall type I family-wise error rate at the one-tailed 0.025 significance level, a multiple-sequence gatekeeping procedure was implemented in a Monte Carlo study with 1000 runs and with the Bonferroni correction applied to the set of superiority comparisons (first gatekeeper) and the Hochberg correction applied to the set of non-inferiority comparisons (second gatekeeper).

For the superiority tests, and with group sample sizes of 100 patients in placebo group and 100 patients in NAC group, the Monte Carlo study estimated an overall power ("disjunctive" power) close to 93% to reach statistical significance in at least one co-primary end-point. These calculations are based on a one-sided Mann-Whitney test and assuming a minimal clinically relevant difference of 0.35 points between placebo and NAC on a 0-3-point scale, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two end-points equal to 0.31.

For the non-inferiority tests, a sample of 100 patients per each active treatment group ensures sufficient disjunctive power (Monte Carlo disjunctive power = 82%) to detect non-inferiority between NAC and ambroxol in at least one co-primary end-point. These calculations are based on a one-sided non-inferiority t-test assuming a margin of non-inferiority equal to 0.30, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two endpoints equal to 0.31.

Assuming a drop-out rate of about 10% over one week of entry, a total of 333 patients will be randomized (i.e. 111 patients in the placebo group, 111 patients in the NAC group and 111 patients in the ambroxol group).

Statistical methods

All efficacy analyses will be performed on the Modified Intention to Treat (mITT) population. Analysis of the primary and secondary efficacy variables will be also carried out on the Per Protocol (PP) population to assess the robustness of the findings. Safety outcomes will be analysed on the Safety population.

The primary efficacy end-points "change from baseline to the 1-week treatment in sputum viscosity score and change from baseline to the 1-week treatment in expectoration difficulty score"

will be analysed by means of stratified Mann-Whitney U Statistic for testing the hypotheses of superiority of NAC versus placebo after blocking for baseline score and by means of the non-inferiority variant of the Mann-Whitney U Statistic for testing the hypotheses of non-inferiority of NAC versus ambroxol. Statistical significant results will be needed on both mITT and PP populations to accept the hypothesis of non-inferiority of NAC versus ambroxol. Point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

The overall type I family-wise error rate for testing the co-primary endpoints in superiority and non-inferiority assessments will be controlled at the one-tailed 0.025 significance level using a multiple-sequence gatekeeping procedure. This procedure will be fully described in the protocol.

The same approach will be taken for the supportive secondary end-point “superiority of NAC over placebo in change from baseline to day 3 of mean sputum viscosity score or mean expectoration difficulty score”.

As for the supportive secondary efficacy end-points concerning individual scores (sputum viscosity, expectoration difficulty, sputum color, cough) or measured on continuous scale (sputum volume), the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (stratified Mann-Whitney U Statistics blocking for baseline score), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

The same statistical analysis (stratified Mann-Whitney U Statistics blocking for baseline score) will be carried out for testing superiority of ambroxol vs placebo on the same efficacy endpoints. Results will be used for the purpose of verifying study’s assay sensitivity.

For the analyses of supportive secondary efficacy end-points no adjustment of significance level will be made to account for multiple comparisons.

Missing data on the primary and secondary efficacy endpoints will be imputed as treatment failures (MVTF) by replacing missing values using the worst observation carried forward (WOCF) as primary imputation method (namely baseline or follow-up measurement, whichever is worse, and using expectation-maximization (EM) algorithm and last observation carried forward (LOCF) as sensitivity analyses.

Concomitant Treatments	**Permitted** • Appropriate treatment(s) for any respiratory tract disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes, such as: corticosteroids (inhaled or systemic), bronchodilators, antibiotics (in case of co-administration, the i.v. antibiotic should be administered separately). • Appropriate treatment(s) for any other underlying disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes • If co-treatment with parenteral nitroglycerin is needed the patients should be monitored for potential hypotension, which may be severe and may be indicated by the presence of headache • If one or more treatments interfering with the measurements contributing to the primary efficacy outcomes are deemed necessary, the patient should not be randomized or should be discontinued from the study. All concomitant medications will be recorded and analysed as described in Section 20.4.3.3. **Not permitted** • Expectorants • Antitussive agents • Sedatives • Traditional Chinese Medicine (TCM) treatments.

4. INTRODUCTION AND RATIONALE

Background

Numerous respiratory diseases, including acute and chronic bronchitis, COPD, cystic fibrosis and non-cystic fibrosis bronchiectasis are characterized by increased sputum viscosity and difficult expectoration, often associated with cough (1- 4).

Furthermore, acute and chronic bronchitis and COPD are commonly associated with of many non-respiratory chronic conditions in both outpatients and hospitalized patients, especially in smokers, elderly patients and patients living in heavily polluted environments.

In China, cigarette smoking, and high environmental pollution have a high prevalence and morbidity (5). Hence, abnormalities of mucus and expectoration are frequent in patients with primary respiratory diseases and with respiratory complications of chronic non-respiratory conditions (6).

Treatment

Mucolytic agents are used worldwide for symptomatic treatment of abnormalities of mucus viscosity and expectoration. These include N-acetyl cysteine, also referred to as NAC (Fluimucil®, Zambon) and ambroxol hydrochloride (Mucosolvan®, Boehringer Ingelheim; Fluibron®, Chiesi Farmaceutici S.a.s.).

NAC exerts an intense mucolytic-fluidifying action on mucous and mucopurulent secretions by depolymerizing mucoproteic complexes and nucleic acids which contribute to the viscosity of sputum and other secretions. In addition, NAC exerts a direct antioxidant action, thanks to its free thiol (-SH) nucleophilic group which can interact with the electrophilic groups of oxidant radicals. Of interest is the finding that NAC protects α1-antitrypsin, an elastase-inhibiting enzyme, from inactivation by hypochlorous acid (HClO), a potent oxidant agent produced by the myeloperoxidase enzyme of activated phagocytes. Moreover, NAC can easily cross the cellular membranes; inside the cell NAC is deacetylated to L-cysteine, an amino acid indispensable for glutathione (GSH) synthesis. GSH, a highly reactive tripeptide found in many animal tissues, is the most important endo-cellular protective agent against oxidant radicals, exogenous and endogenous, as well as against several cytotoxic substances (7)

NAC is approved in China for aerosol administration (8) and broadly used by this route of administration as mucolytic agent. However, especially in hospital settings, in China there is a preference to use mucolytic agents by intravenous administration in patients with moderate to severe abnormalities of mucus viscosity and expectoration: intravenous administration is considered by hospital staff more convenient due to common use of other intravenous treatments and is preferred by patients. Hence, the lack of approved NAC for intravenous administration in China is an important gap in medical practice.

Intravenous administration of NAC is approved in most countries at very high doses as an antidote against liver injury due to paracetamol intoxication (see Section 5) (9) and in several countries, namely as mucolytic agent (10). More detail is provided in the Investigator Brochure (IB).

The efficacy and safety of iv infusion of NAC as mucolytic was investigated in seven clinical trials, 3 of which randomized and controlled (11-13) and 4 uncontrolled (14-17).

Trial Rationale

This trial is intended to provide pivotal (phase III) evidence of efficacy and safety for registration in China of slow intravenous infusion of NAC in adult hospitalised patients with respiratory tract diseases and abnormal mucus secretions. NAC, the active test treatment, will be compared to placebo and to ambroxol hydrochloride. The inclusion of a placebo arm is deemed ethically and scientifically sound for the following reasons: 1) the selection criteria used in this study ensure that condition being studied is not serious or life threatening at the time of enrolment; 2) immediate discontinuation from the trial and rescue use of mucolytics is envisaged in the protocol; 3) the true

value of iv intervention in the target population is not fully established. The use of placebo was requested by the Chinese FDA (C-FDA) reviewers in their feedback to an earlier version of this protocol. Ambroxol hydrochloride is included as the third treatment arm of the study as it is the only mucolytic agent approved in China for iv administration. The inclusion of an active control arm, also requested by C-FDA reviewers, will allow to test internal validity of the trial.

This trial is designed as rater- and patient-blind. i.e. whereas the staff administering the study drugs will know what each patient is receiving, neither the staff evaluating the patient, nor the patients themselves will know. The trial cannot be fully blinded (double-blind) because the appearance of NAC ampoules and ambroxol vials is different and more importantly because the NAC formulation releases a harmless but immediately distinguishable sulfuric smell. Rater- and patient-blinded designs are accepted for pivotal registration trials by the US-FDA, EMA and Regulatory Authorities worldwide in situations where full blinding is impossible.

The selected doses of iv NAC and ambroxol are within the limits of relevant SmPCs (10,18); dose justification is provided in Section 5 below.

The treatment duration of 1 week has been selected after consultation with Chinese experts, as only a small minority of patients receive iv mucolytics for more than 1 week.

5. EVALUATION OF THE ANTICIPATED RISKS/BENEFIT RATIO

NAC has been available to patients as a mucolytic agent for many years and has a well-established and satisfactory safety and tolerability profile (see IB).

Independently of route of administration (inhalation, oral, intravenous) adverse events are reported rarely following NAC administration and are usually mild and transient.

The most frequent adverse events associated with NAC oral administration are gastrointestinal (e.g., vomiting, diarrhoea, stomatitis, abdominal pain and nausea). Hypersensitivity reactions (e.g. anaphylactoid reactions, urticaria, rash, pruritus, and bronchospasm) have been reported less frequently after oral administration, while with the IV administration they were reported more frequently compared to gastrointestinal symptoms. Some of the hypersensitivity reactions were associated to higher infusion rate. Most anaphylactoid reactions can be managed by temporarily suspending the acetylcysteine infusion, administering appropriate supportive care. A cumulative analysis of all safety reports received by the Sponsor up to September 2017 for NAC IV, confirmed the nature and severity of the events were in line with the above profile of the product.

Intravenous NAC has been studied in clinical trials and published case series both as mucolytic agent and as an antidote against intoxication by paracetamol and other toxic agents including amanita phalloides and chlorinated hydrocarbons. Overall, in published studies in humans, a total of 745 patients were exposed to iv NAC at doses ranging from 500 mg/day to 980mg/kg/day for a duration of 1 to 18 days. Details of safety results are included in the IB.

In published studies, whereas iv NAC as mucolytic agent typically was given at doses up to 1000 mg/day, much higher iv doses of NAC as antidote were given over multiple days, maintaining a satisfactory safety profile.

Locatelli and colleagues (19) published two case series, one of 86 patients with acute intoxication from amanita phalloides and the other of 35 patients with acute intoxication from chlorinated hydrocarbons. Patients received iv NAC 300 mg/kg/day for 3 to 14 days and 3 to 18 days respectively. The safety and tolerability profile were overall benign, with 4 out of 121 exposed patients suffering from anaphylactoid reaction or rash (due to the rapid administration of the bolus

according to the authors), none of which caused discontinuation of treatment. No other AEs were reported.

Keays and colleagues (20) randomized 50 patients suffering from paracetamol intoxication and admitted to the liver failure unit to NAC in addition to conventional intensive liver care (N=25) or conventional intensive liver care alone (N=25) with maintenance dose of 100 mg/kg/day for several days, until recovery from encephalopathy or death (the average number and range of treatment days is not reported but in survivors appears to be at least 4 days). No AEs were reported in the patients treated with NAC.

From the data summarized above and the full dataset summarized in the IB, a daily intravenous dose NAC of 1200 mg/day given in a hospital setting for 7 days is likely to be associated with a small safety risk.

The safety profile of the active comparator ambroxol hydrochloride given intravenously as is also favourable, as outlined in the Chinese PI. The product is well tolerated, and mild upper gastrointestinal adverse reactions have been occasionally reported, mainly including stomach burning, indigestion and occasional nausea and vomiting, occurring mostly after parenteral administration. Allergic reactions are rare, mainly including rash. Few cases have reported severe acute allergic reactions, but the correlation with ambroxol hydrochloride is not known. The dose chosen for this trial (60 mg/day) is within the range allowed by the Chinese SmPC (18).

Anticipated benefits to the patients with respiratory tract diseases and abnormal mucus secretions randomised to NAC and ambroxol hydrochloride include reduction in mucus viscosity and improved expectoration.

In conclusion, for both active treatments, in this trial the benefit risk ratio is anticipated to be positive.

Patients randomized to placebo will be monitored very closely by experienced investigators and study staff. Should expectoration difficulty increase during the trial, the investigator and/or the patient may choose to discontinue the study treatment and immediately administer/receive rescue mucolytic, as described in Sections 8.1 and 10.10. Hence, also for the patients randomized to placebo no clinically meaningfully negative benefit/risk ratio is anticipated.

6. OBJECTIVES

The primary objective of this trial is to demonstrate that slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score in adult Chinese hospitalized patients with respiratory tract diseases and abnormal mucus secretions.

Secondary objectives are as follows:
Efficacy
Demonstrate in the same patient population that:

- slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is superior to placebo in change from baseline to day 3 and end of 1-week treatment of other indicators of mucolytic activity: individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume;
- slow (at least 5 minutes) intravenous infusion of NAC 600 mg twice daily is non-inferior to slow intravenous infusion of ambroxol hydrochloride 30 mg twice daily in change from baseline to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score;
- slow (at least 5 minutes) intravenous infusion of ambroxol hydrochloride 30 mg twice daily is superior to placebo in change from baseline to day 3 and to the end of 1-week treatment of sputum viscosity score or expectoration difficulty score and of other indicators of mucolytic

activity: individual sputum viscosity and expectoration difficulty scores, cough score, mucous color score and mucous volume.

Safety

Confirm that 1-week treatment with iv NAC 600 mg twice daily is safe and well tolerated.

The trial endpoints are described in Section 20.2.

7. ETHICS REQUIREMENTS

This trial will be conducted in compliance with last version of Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html), with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), in particular E6(R2), with the applicable regulatory requirements and with Zambon and contract research organisation (CRO) standard operating procedures (SOPs).

8. DESIGN AND DURATION OF THE CLINICAL TRIAL

8.1. CLINICAL TRIAL DESIGN

This is a multicenter, randomized, rater- and patient-blind, placebo- and active-controlled, 3-arm parallel group clinical trial.

The trial will be conducted in approximately 25 sites in China.

Please refer to Appendix 1 for a trial flow chart.

The study will consist of a total of 4 core hospital visits (screening, baseline, treatment day 3, treatment day 7, see Section 10) and of one follow-up phone call 2 weeks after discontinuation of treatment; if the patient is still hospitalized or if more convenient for the patient, the follow-up phone call can be replaced by a follow-up hospital visit.

At screening visit (Visit 1), patients will be asked to provide Informed Consent prior to any trial related procedure and will be checked against inclusion and exclusion criteria. Their medical history will be recorded. Furthermore, patients will undergo a 12-lead ECG and laboratory assessments. Results must be available before Visit 2.

At randomization visit (Visit 2), to occur within 7 days after Visit 1, female patients will undergo a pregnancy test; all patients will be checked again against the full set of inclusion and exclusion criteria and eligible subjects will be randomised with a 1:1:1 ratio to receive NAC or ambroxol hydrochloride or placebo.

A total of 111 patients are to be randomized in each treatment group.

Procedures performed at each core hospital visit will include documentation of concomitant medications and treatment emergent adverse events (TEAEs), 24-hour sputum collection and assessment on a 4-point ordinal scale of expectoration difficulty, sputum viscosity, sputum color and cough.

In case a patient experiences a deterioration of expectoration capacity and related symptoms, and/or of an underlying condition, he/she should contact a study investigator immediately and undergo an unscheduled deterioration visit. If the patient and/or the investigator believe that it is in the patient's best interest to receive a rescue mucolytic, the patient will be discontinued from the study and rescue mucolytic will be administered, with any additional treatment the investigator deems appropriate.

8.2. DURATION OF CLINICAL TRIAL

The overall study duration (from first patient first visit to last patient last visit) is expected to be of approximately 8 months.

The maximum expected duration of participation in this trial for an individual subject, from Visit 1 (Screening) to the follow-up phone call or visit is 4 weeks. Treatment duration will be 1 week (7days).

The start of the trial is defined as first subject in, i.e. Visit 1 for the first subject.

The end of the trial is defined as the last subject out, i.e. when the last subject had the follow-up phone call or follow-up visit or unscheduled Deterioration visit.

If the trial is prematurely stopped, please refer to Section 17.

9. CLINICAL TRIAL POPULATION

9.1. NUMBER OF SUBJECTS

A total of 333 subjects (111 in each treatment group) is planned to be enrolled into the trial. The enrolment is competitive among sites.

For a description of sample size calculation, please refer to Section 20.3.

9.2. SELECTION OF SUBJECTS

9.2.1. INCLUSION CRITERIA

Subjects can be enrolled in the trial if they meet all inclusion criteria listed below:

1. Male or female adult (≥18 years old) hospitalized patients with respiratory tract diseases and abnormal mucus secretions such as: acute bronchitis, chronic bronchitis and exacerbations, emphysema, mucoviscidosis and bronchiectasis. Diagnostic criteria for these conditions are provided in Annex 1
2. Chinese ethnicity and/or Chinese
3. Signed the informed consent form before any study-related procedure
4. Sputum viscosity score ≥ 2 at randomization visit
5. Expectoration difficulty score ≥ 2 at randomization visit
6. Willingness and ability to comply with study procedures

9.2.2. EXCLUSION CRITERIA

Subjects are not eligible for the trial if they meet one or more of the exclusion criteria listed below:

1. Intolerance or contra-indication to treatment with NAC or ambroxol or allergy to any component of the study treatments
2. (For female patients) ongoing pregnancy or lactation, or childbearing potential but unwillingness to adopt abstinence or contraception measures during the study
3. Intake of an investigational drug within 1 month before the screening visit
4. Use of expectorants or drugs with expectorant effect within 2 days before randomization visit

5. Diagnosis of active tuberculosis, lung cancer, pulmonary fibrosis, acute pulmonary thromboembolism or any other respiratory condition that might, in the opinion of the investigator, compromise the safety of the patient or affect the interpretation of the results
6. Medical history of and/or illness (including laboratory abnormalities) and/or treatment that in the investigator's opinion may interfere with the patient's safety, compliance, or study evaluations
7. Serum ALT and/or AST more than 3 times above the upper limit of normal at screening visit
8. Serum creatinine more than 3 times above the upper limit of normal at screening visit
9. Addiction to alcohol or drugs
10. Mental illness, or other reasons for non-cooperation in the investigator's opinion

Contraceptive methods

Although teratology studies carried out in animals evidenced no teratogenic effects of NAC (ref IB) or ambroxol hydrochloride (ref Package Insert China), safety in human pregnancy has not been established with iv administration.

Female subjects can be enrolled if they are either post-menopausal for at least 2 years, or surgically sterilized or have undergone hysterectomy.

Female subjects of child-bearing potential must be willing to avoid pregnancy. They are required to have a negative pregnancy test at inclusion (see Section 10.2), and should use a highly effective method of birth control for 1 month prior to randomisation, throughout the trial duration and up to 1 month after the last dose of IMP, which include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- surgical sterilization (e.g. bilateral tubal ligation or occlusion)
- male sterilization (vasectomised partner)
- sexual abstinence
- a male sexual partner who agrees to use a male condom with spermicide

Throughout the course of the study male participants with female partners of child bearing potential must abstain from sexual intercourse or use condoms or use effective contraceptive precautions (female partners should follow the same birth control of female patients).

Male participants must also not take part in the donation of sperm whilst enrolled on the study.

10. OVERALL CLINICAL TRIAL SCHEDULE

The current trial will include 4 planned core clinical visits at the investigational site and 1 follow-up telephone call or visit. Unscheduled Deterioration visit(s) will be conducted as necessary. A detailed flow chart showing the procedures performed is given in Appendix 1. The following sections outline the procedures to be performed at the individual visits.

10.1. VISIT 1 - SCREENING VISIT

At Visit 1 (Screening), the following procedures will be performed:

- obtain written Informed Consent before any study-related procedure;
- document medical history and subject's demographic data;
- document concomitant medications;
- assess vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- conduct 12-lead ECG in the supine position after 5 minutes of rest (Section 11.1.6);
- check inclusion/exclusion criteria: not all criteria can be assessed at screening, but do not proceed further if the patient is not eligible based on the criteria that can be checked;
- collect blood samples for clinical laboratory assessments (haematology and clinical chemistry). (Section 11.1.4);
- Instruct patients on actions to be taken in case of worsening of symptoms related to expectoration.
- Record details of any AEs since the Inform Consent signature

The Investigator will arrange an appointment for Visit 2 within 7 days.

10.2. VISIT 2 - RANDOMISATION VISIT (DAY 1) - (WITHIN 7 DAYS OF VISIT 1)

At Visit 2 (Randomisation), the following procedures will be performed:

- conduct dip-stick urine pregnancy test for females of childbearing potential.
- check complete set of inclusion and exclusion criteria;
- document concomitant medications;
- record details of any AEs since the Screening Visit (Visit 1);
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- give to patient the container for 24-hour sputum collection and instruct patient to collect all sputum until the same time of the following day;
- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided;
- randomise the eligible patient by IWRS;
- administer first dose of study medication in the morning and the second dose in the afternoon/evening. The two daily doses must be administered approximately 12 hours apart from each other.
- Warning: Study staff responsible for administration of study medication, patient care and routine assessments (unblinded) should be different from study staff responsible for rating of expectoration difficulty, sputum viscosity, sputum color and cough (rater). No disclosure of the identity of study medication from the former to the latter is to occur unless required for safety reasons;
- remind patients on actions to be taken in case of worsening of symptoms related to expectoration.
- To assess adherence with IMP dosing regimen

The Investigator will arrange an appointment for Visit 3 (on day 3 after Visit 2) and will instruct the subjects to report any AEs occurring during this period at the next visit.

10.3. DAY 2

On day 2 the following procedures will be performed:

- collect 24-hour sputum sample and report volume (mL) in eCRF;
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

10.4. VISIT 3 (DAY 3)

At Visit 3 (day 3), the following procedures will be performed:

- document concomitant medications;
- record details of any AEs since the Randomization Visit (Visit 2);
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- give to patient the container for 24-hour sputum collection and instruct patient to collect all sputum until the same time of the following day;
- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above);
- remind patients on actions to be taken in case of worsening of symptoms related to expectoration. To assess adherence with IMP dosing regimen

The Investigator will arrange an appointment for Visit 4 (on day 7 after Visit 2) and will instruct the subjects to report any AEs occurring during this period at the next visit.

10.5. DAY 4

On day 4 the following procedures will be performed:

- collect 24-hour sputum sample and report volume (mL) in eCRF;
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

10.6. DAYS 5 AND 6

On days 5 and 6 the following procedure will be performed:

- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

10.7. VISIT 4 (DAY 7)

At Visit 4 (day 7), the following procedures will be performed:

- conduct dip-stick urine pregnancy test for females of childbearing potential.
- document concomitant medications;
- record details of any AEs since Visit 3 (day 3);
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- give to patient the container for 24-hour sputum collection and instruct patient to collect all sputum until the same time of the following day;

- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided.
- conduct 12-lead ECG in the supine position after 5 minutes of rest (Section 11.1.6);
- collect blood samples for clinical laboratory assessments (haematology and clinical chemistry).
- to assess adherence with IMP dosing regimen
- administer study medication at the same times as on Day 1 (see Warning in section 10.2. above).

The Investigator will arrange an appointment for the follow-up call or visit 2 weeks ± 3 days after the last administration of IMP

10.8. DAY 8

On day 8 the following procedure will be performed:

- collect 24-hour sputum sample and report volume (mL) in eCRF;

10.9. FOLLOW-UP PHONE CALL OR VISIT (2 WEEKS ± 3 DAYS AFTER THE LAST ADMINISTRATION OF IMP)

A follow-up phone call will be performed at 2 weeks ± 3 days after the last administration of IMP. If the patient is still hospitalized or it is more convenient for the patient, the follow-up call can be replaced by a follow-up visit

The following procedures will be performed during the follow-up call or visit:

- record details of any AEs since Visit 4 (day 7);
- record concomitant medications since Visit 4.

10.10. UNSCHEDULED DETERIORATION VISIT

Patients will be trained by the Investigator to recognise worsening of expectoration and related symptoms.

If the patient and/or the investigator believe that it is in the patient's best interest to receive a rescue mucolytic, the patient will be discontinued from the study and rescue mucolytic will be administered, with any additional treatment the investigator deems appropriate and an unscheduled Deterioration Visit should be conducted whenever possible.

An unscheduled Deterioration Visit should be conducted also in case of worsening of the underlying condition. In particular, in case of bronchospasm in asthmatic patients the treatment must be discontinued and adequate therapeutic measures taken.

In case of unscheduled Deterioration Visit the following procedures will be performed:

- record details of any AEs since previous visit
- conduct dip-stick urine pregnancy test for females of childbearing potential.
- assess of vital signs (Section 11.1.3);
- conduct physical examination (including chest auscultation);
- conduct 12-lead ECG in the supine position after 5 minutes of rest (Section 11.1.6);
- conduct assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided

In case during the unscheduled deterioration visit the patient and/or the investigator deem appropriate the discontinuation from the trial, all evaluations requested at Visit 4 should be performed (Section 10.11).

10.11. PREMATURE DISCONTINUATION VISIT

In case of premature discontinuation for any other reasons than those listed in 10.10 all evaluations requested at Visit 4 should be performed, excluding study medication administration.

A premature discontinuation visit must also be conducted in case of unexpected pregnancy.

11. METHODOLOGY

11.1. METHODS OF ASSESSMENT

11.1.1. DEMOGRAPHY AND MEDICAL HISTORY

At Visit 1 (Screening) the subjects' demographic data will be documented, including age, ethnicity, gender, height, weight as well as smoking history and alcohol use.

Further, the reason for hospitalization and medical history will be documented.

Any relevant worsening in ongoing conditions during the trial (i.e. since Visit 1) is required to be recorded as AEs in the eCRF (see Section 18).

11.1.2. PHYSICAL EXAMINATION

At Visit 1, Visit 2, Visit 3 and Visit 4, and/or at the unscheduled deterioration Visit/premature discontinuation, a physical examination of general body systems will be performed according to current medical standards and site practice. The examination is to include a chest auscultation. Any relevant worsening regarding physical examination results of a subject since Visit 1 should be recorded as AE in the eCRF (see Section 18).

11.1.3. VITAL SIGNS

At Visit 1, Visit 2, Visit 3 and Visit 4 and/or at the unscheduled deterioration visit/premature discontinuation, vital signs will be recorded according to site practice. Vital signs include:

- heart rate,
- systolic and diastolic blood pressure, measured after at least 5 minutes in the supine position,
- respiratory rate,
- body temperature, measured under the arm pit.

Automatic or manual devices may be used, but the same device should be used for any given subject throughout the trial. The same arm should be used for all measurements.

Any relevant clinically significant worsening of vital signs of a subject since the previous visit should be recorded as AE in the eCRF (see Section 18).

11.1.4. LABORATORY EVALUATIONS

Routine laboratory evaluations will be performed at Screening Visit (Visit 1) and Visit 4 and in case of premature discontinuation.

The blood samples must be collected after the 12-lead ECG has been performed.

The haematology and clinical chemistry parameters detailed in Table 1 will be analysed by the local hospital laboratory.

Subjects with clinically relevant impaired renal function, as defined by serum creatinine levels ≥3.0x upper limit of normal at Visit 1 will not be randomized.

Subjects with clinically relevant impaired liver function, as defined by serum ALT and/or AST ≥3.0x upper limit of normal at Visit 1 will not be randomized.

A dipstick urine pregnancy test for women of childbearing potential will be performed at Randomization Visit (Visit 2) and at Visit 4 and/or at unscheduled deterioration visit/premature discontinuation visit.

Female subjects who become pregnant during the trial must be withdrawn from the trial without delay and undergo the premature discontinuation visit; these patients are to be followed up to determine the outcome of the pregnancy. The Investigator is required to inform the Sponsor of a subject's pregnancy and the estimated date of delivery. Reporting requirements are outlined in Section 18.10.

Clinical laboratory tests will be reviewed for results of potential clinical significance before Visit 2 to confirm patient's eligibility and during the trial, as appropriate. Clinically significant laboratory abnormalities arising at Visit 4 (or at premature discontinuation visit) are considered AEs. Where possible, a diagnosis should be ascribed to the abnormal lab test.

Table 1 CLINICAL LABORATORY EVALUATIONS

Hematology: at Screening Visit (Visit 1) and Visit 4 or premature discontinuation visit			
Hematocrit	Hemoglobin	Platelet count	Red blood cell count
White blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils)			
Clinical Chemistry: at Screening Visit (Visit 1) and visit 4 or premature discontinuation visit			
BUN or UREA	Chloride	AST	
Creatinine	Uric acid	ALT	
Sodium	Amylase	γGT	
Potassium	ALP	Bilirubin (direct and total)	
Calcium			
Pregnancy Test: at Screening Visit (Visit 1), Visit 4 or premature discontinuation visit			
Urine β-hCG (dipstick)			

11.1.5. EFFICACY EVALUATIONS

Sputum viscosity, expectoration difficulty, sputum color, cough

Sputum viscosity, expectoration difficulty, sputum color and cough are assessed by means of ordinal categorical 4-point scales with 0 = best and 3 = worst.

For each patient the assessment is to be carried out by the blinded rater on treatment days 1 (baseline), 3 and 7 in the morning before 9 am before administration of study drug. Should a patient discontinue prematurely from the trial (including discharge from the hospital before day 7) an assessment should be conducted on the day of discontinuation whenever possible (see unscheduled Deterioration Visit, Section 10.10).

Scoring criteria are as follows (adapted from [12])

	0	1	2	3
Sputum viscosity	Liquid (normal viscosity)	Fluid (mildly increased viscosity)	Viscous (moderately increased viscosity)	Sticky (severely increased viscosity)
Expectoration difficulty	No difficulty	Mild difficulty	Moderate difficulty	Marked difficulty
Sputum color	Mostly white	Mostly pale yellow	Mostly dark yellow	Very dark yellow /green
Cough	No cough	Sporadic and mild cough	Moderate cough	Severe Cough

Sputum Volume

At Randomization Visit (Visit 2), Visit 3 and Visit 4 the patients will be given a graduated container and instructed to use it to collect all sputum generated in the following 24 hours (i.e. same time of the following day). The day the container will be collected, and the 24-hour sputum volume measured in ml.

11.1.6. SAFETY EVALUATIONS

Adverse Events

AEs will be recorded by Investigator in the appropriate eCRF Section from Visit 1 (date of informed consent) to the follow-up phone all or visit occurring 2 weeks (±3 days) after the last administration of the investigational medicinal product (IMP). At each contact (i.e. clinical visit or phone call), subjects will be asked in a non-leading manner if they experienced any AEs.

All AEs occurring from the day of the first IMP administration, i.e. Visit 2, until the end of the trial, i.e. follow-up phone call, will be considered as treatment emergent TEAEs.

For definitions and reporting of AEs and SAEs, see Section 18.

12-lead electrocardiogram (ECG)

12-lead ECG recordings will be obtained at each study centre using site machines at the Screening Visit (Visit 1) to verify the eligibility of the subject, and at Visit 4 or unscheduled Deterioration visit.

ECG will be performed after obtaining vital signs. Prior to recording, the subject should be at rest for at least 5 mins.

ECG will be evaluated by the investigator/local medical staff and the recording will be reported in the eCRF as “normal”, “abnormal clinically significant” or “abnormal not clinically significant”.

Abnormalities of clinical significance recorded at Visit 1, Visit 4 or unscheduled deterioration visit/premature discontinuation visit which are not related to pre-exist medical condition before ICF signature will be reported as AEs. Repeat measurements will be performed if needed.

11.2. ADHERENCE WITH IMP DOSING REGIMEN

As the administration of the IMP will be carried out by the study staff in a hospital setting, it is anticipated that adherence with IMP dosing regimen will be high.

Nevertheless, the Investigator will assess adherence with IMP dosing regimen on an ongoing basis by determining the amount of IMP dispensed, used (i.e. returned open ampoules/vials) and the amount of IMP returned (i.e. returned, unopened ampoules/vials) at Visit 2 (first dose), Visit 3 and Visit 4 (end of treatment) or unscheduled Deterioration Visit/premature discontinuation visit.

The evaluation of compliance will be done using the following formula:

$$\% \text{ of administered drug} = 100 \times \frac{\text{Total number of administered doses}}{\text{Total number of scheduled doses}}$$

11.3. PHARMACODYNAMICS

Not applicable.

11.4. PHARMACOKINETICS

Not applicable.

12. PRIOR AND CONCOMITANT TREATMENTS

At Visit 1 (Screening), all prior and concomitant medications, including antibiotics, and over-the-counter products used by an individual subject within 1 month prior to Screening Visit (Visit 1) will be documented in the eCRF.

During all subsequent clinical visits, the Investigator will document any changes in concomitant medications.

The following concomitant treatments are permitted from Visit 1 to Visit 4 (end of IMP treatment) or unscheduled Deterioration Visit:

- Appropriate treatment(s) for any respiratory tract disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes, such as: corticosteroids (inhaled or systemic), bronchodilators, antibiotics (in case of co-administration, the i.v. antibiotic should be administered separately).
- Appropriate treatment(s) for any other underlying disease, that in the investigator's opinion will not interfere with the measurements contributing to the efficacy outcomes
- If co-treatment with parenteral nitroglycerin is needed the patients should be monitored for potential hypotension, which may be severe and may be indicated by the presence of headache
- If one or more treatments interfering with the measurements contributing to the primary efficacy outcomes are deemed necessary, the patient should not be randomized or should be discontinued from the study

The following concomitant treatments are not permitted from Visit 1 to Visit 4 (end of IMP treatment) or unscheduled Deterioration Visit:

- Expectorants
- Antitussive agents
- Sedatives
- Traditional Chinese Medicine (TCM) treatments.

All concomitant medications will be recorded and analysed as described in Section 20.4.3.3.

13. INVESTIGATIONAL MEDICINAL PRODUCT

13.1. INVESTIGATIONAL MEDICINAL PRODUCT SUPPLIES AND PACKAGING

NAC will be supplied in boxes containing 4 ampoules each.

NAC is formulated in yellow glass ampoules as a solution of 300 mg NAC in 3 ml water for injection; other excipients are: sodium hydroxide and disodium edetate. The product is manufactured by Zambon SpA, Vicenza, Italy.

Ambroxol hydrochloride will be supplied in boxes containing 4 vials each.

Ambroxol hydrochloride is formulated in yellow glass vials as a solution of 15 mg ambroxol hydrochloride in 2 ml water for injection; other excipients are: citric acid monohydrate, sodium hydrogen phosphate dihydrate, sodium chloride. The product is manufactured by Boehringer Ingelheim.

Placebo will be supplied in boxes containing 2 vials each.

Placebo is formulated in vials as 10 ml NaCl 0.9% saline solution. The product is manufactured by China Otsuka Pharmaceutical Co., Ltd.

13.2. INVESTIGATIONAL MEDICINAL PRODUCT DISPENSING AND ADMINISTRATION

All IMPs will be dispensed twice daily as one in the morning and another is in the afternoon/evening for a week of treatment period at hospital investigational sites by study staff. All IMP will be administered at the hospital investigational sites by study staff otherwise not involved with the efficacy assessment and care of study patients. The study staff members administering the IMP will be aware of its identity but will not disclose it to patients or to other study staff members who are involved in efficacy assessment (patient and rater-blind design, see Section 4).

NAC (Active test treatment)

Two ampoules (NAC 600 mg) will be diluted in 10 ml NaCl 0.9% saline solution and administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 ± 1 hours apart for 1 week (7 days). Total daily NAC dose: 1200 mg/day.

Ambroxol hydrochloride (active control treatment)

Two vials (ambroxol 30 mg) will be diluted in 10 ml NaCl 0.9% saline solution and administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 ± 1 hours apart for 1 week (7 days). Total daily ambroxol dose: 60 mg.

Placebo

One vial of 10 ml NaCl 0.9% saline solution will be administered by slow (at least 5 minutes) intravenous infusion twice a day, morning before 9 am and afternoon/evening approximately 12 ± 1 hours apart for 1 week (7 days).

Study staff administering the IMP will be instructed to store the empty used and the unused ampoules/vials for IMP accountability.

13.3. RANDOMISATION

Each subject will receive a screening number as soon as site staff enters the IWRS, after they have signed the ICF (Visit 1).

The screening number will consist of country number (1 digit), a site number (3 digits) and a continuous number for a subject at an individual site (3 digits), e.g. 1001001. Every subject who signs the ICF must be entered into the IWRS system regardless of eligibility.

At Visit 2, eligible subjects will be randomised using the IWRS according to a pre-specified randomisation scheme such that they either receive NAC or ambroxol hydrochloride or placebo.

The randomisation within each site will be done with blocks sized of unequal length to guarantee a good balance among NAC, ambroxol hydrochloride and placebo at any stage of the enrolment minimizing the procedure selection bias.

The allocation to the treatment will be stored within the IWRS database until unblinding of the trial is requested. Unblinding may be performed directly by the Investigators only in case of SAE of life-threating significance where knowledge of treatment assignment is essential for the future management of patient care (see Section 15.1).

13.4. INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

IMP inventory and accountability records will be maintained within IWRS. The following rules are to be followed:

a) The Investigator will keep IMPs in a pharmacy, or a locked and secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the IMPs.

b) The inventory will be maintained by the Investigator or pharmacist or other nominated individual. The inventory will be done by means of a specific “Subject/Study Investigational Product Accountability Record & Investigational Product Reconciliation Log” and will include details of IMPs received and a clear record of when they were dispensed.

c) At the conclusion or termination of the clinical trial, the Investigator will conduct a final IMP inventory and to record the results of the inventory on an Investigational Product Return Form. The monitor will check that IMP accountability was correctly performed. The Investigator will return all original IMP containers, whether empty or full, to the CRO for final reconciliation and destruction.

d) The Investigator/pharmacist agree not to supply IMP to any person except those named as Investigators/Co-Investigators as detailed in the Site Signature/Delegation Log, and to subjects in this trial.

For instructions to maintain the study patient and rater-blind, see Section 4.

14. CLINICAL TRIAL AMENDMENTS

Changes to the CTP can be made preparing written amendments to be agreed and signed by the Principal Investigator and Sponsor. No substantial amendment can be implemented without a favourable opinion of the Ethics Committee (EC) and Competent Authority (CA) and CA, unless the changes consist of urgent safety measures to protect trial subjects.

Amendments which are non-substantial amendments as defined by current regulations can be sent to EC/CA for notification as applicable per local requirements and may be implemented at the site before EC notification according to local rules.

15. DEVIATIONS FROM THE CLINICAL TRIAL PROTOCOL

Any major or critical deviation which may have an impact on study results and/or the safety of the subjects should be immediately reported to the CRO and a decision will be taken together with the Sponsor whether or not the patient for whom the deviation from the CTP took place is to continue in the trial. A deviation log will be maintained to track actual deviations and decisions taken. All deviations will be reported to the EC and CA according to ICH-GCP and local requirements.

In case of an emergency deviation from the CTP has to be implemented for a give patient, this deviation will be only applied to that individual.

In such an emergency the Investigator must contact the CRO by telephone as soon as possible.

15.1. CODE BREAKING

The code for any individual subject will not be broken by the Investigator/rater during course of the trial except in the circumstance of an SAE where knowledge of treatment assignment is essential for the future management of patient care.

Despite the fact that this study is not double-blind, in order to ensure proper documentation, in case of emergency, unblinding of the treatment is to be done through IWRS. The IWRS will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the site users. Site users will be provided with usernames and passwords to access the IWRS. Unblinding of the study treatment must be done in case of an emergency situation, where the Investigator/rater considers it essential to know what treatment the subject was taking. Access to the unblinding option will be granted only to the Investigators and sub-Investigators at the sites. The IWRS will promptly notify the Sponsor and the Clinical Trial Monitor whenever a treatment code is unblinded. If the treatment code has been opened, this must be recorded in the eCRF.

Users from PAREXEL and Sponsor Pharmacovigilance will have their own passwords to unblind subjects in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the CA and ECs.

16. CLINICAL TRIAL WITHDRAWALS/DROP-OUTS

Patients will be withdrawn from the trial for one of the following reasons:

- patient may withdraw from the study at any time at his/her own request;
- patient may withdraw from the study due to an AE;
- patient may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative reasons;
- patient may be withdrawn due to lack of adherence to study medication regimen.
- Female patient who becomes pregnant should be withdrawn from the trial and followed-up in accordance with Section 18.8;
- Patient should be withdrawn from the trial once rescue mucolytic is received;
- non-emergency unblinding of study treatment allocation;
- lost to follow up: before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study;

The sponsor, CA, or EC/IRB(s), can terminate the trial or participation of an individual site.

The reason for removal of a subject from the trial or premature discontinuation of treatment must be fully documented in the eCRF as well as in respective source documents. Follow-up for withdrawn subjects follows the procedures described in Section 18.8 and Section 18.9.

17. STOPPING AND DISCONTINUATION CRITERIA FOR THE TRIAL

The trial may be prematurely terminated or placed on temporary hold for the following reasons:

- the Sponsor feels that the number and/or severity of AEs justifies discontinuation of the trial;
- the Sponsor considers the applied doses of one or more IMPs to be no longer relevant;
- data not known before, become available and raise concern about the safety of one or more IMPs so that continuation would pose potential risks to the subjects;

Premature termination of the trial must be reported to the EC and CA according to applicable laws generally within 30 days. A detailed written explanation of the reason should be given and alternative procedures for subjects under treatment specified.

However, trial results have to be reported according to the requirements outlined in this CTP as far as applicable.

If, after the termination of the trial, the risk/benefit analyses have changed, the new evaluation should be provided in case it will have an impact on the planned follow-up of the patients who have participated in the trial. If possible, the patients should return to the clinic for an early End of Treatment Visit.

18. REPORTING SAFETY INFORMATION

18.1. DEFINITION OF ADVERSE EVENT

An AE is "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".

AEs include:

- worsening (change in nature, severity or frequency) of conditions present at the onset of the trial;
    - worsening of expectoration difficulties and related symptoms may prompt discontinuation of the patient and immediate administration of rescue mucolytic if judged to be in the patient's best interest by the investigator and/or the patient him/herself
- subject deterioration due to the primary illness;
- intercurrent illnesses;
- drug interactions;
- events related or possibly related to concomitant medications;
- abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the IMP.

An unscheduled Deterioration Visit should be conducted whenever possible (Section 10.10).

18.2. DEFINITION OF ADVERSE EVENT OF SPECIAL INTEREST

No AEs of special interest are defined for this trial.

18.3. DEFINITION OF ADVERSE DRUG REACTION

An adverse drug reaction (ADR) is “any untoward and unintended response to an IMP related to any dose administered and which implies an AE with at least a reasonable possibility of a causal relationship with the use of the product (i.e. there is evidence or arguments to suggest a causal relationship).

The definition covers also medication error and uses outside what is foreseen in the CTP, including misuse and abuse of the IMP.

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

18.3.1. DEFINITION OF UNEXPECTED ADVERSE DRUG REACTION

An unexpected ADR is: “An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure [IB] for an unapproved investigational product or SmPC, for approved product)”. The reference safety information for evaluation of AE expectedness in this trial will be the Investigator Brochure for NAC and the Chinese Package Insert for ambroxol hydrochloride.

18.4. DEFINITION OF SERIOUS ADVERSE EVENTS OR SERIOUS ADVERSE DRUG REACTIONS

18.4.1. DEFINITION OF SERIOUS ADVERSE EVENT OR SERIOUS ADVERSE REACTION

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening (i.e. the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing hospitalisation considering that hospitalization is not a SAE in itself, planned or selective hospitalization, hospitalization for underlying disease which did not worsen during the study, as well as hospitalizations for social reasons should not be reported as SAEs;
- results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement);
- is a congenital anomaly/birth defect;
- is an important medical event that may not result in death, be life-threatening, or require hospitalisation but, according to appropriate medical judgment, it may jeopardise the subject and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

A Serious Adverse Reaction (SAR) is any SAE judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product.

18.4.2. DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs/SARs that, although foreseeable, are potentially related to the IMP and not identified in the reference safety information and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

18.5. DEFINITION OF SEVERITY OF ADVERSE EVENTS

The term “severe” is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the subject may experience slight discomfort;
- Moderate: causing some limitation of usual activities; the subject may experience annoying discomfort;
- Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

18.6. DEFINITION OF ADVERSE EVENT CAUSALITY

Causality shall be determined according to the definition of ADRs as given in Section 18.3.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as ADRs. The causality assessment given by the Investigator should not be downgraded by the Sponsor.

The following binary decision for causality will be used:

- reasonable possibility that the IMP caused the event;
- no reasonable possibility that the IMP caused the event.

Features supportive of an association include:

- temporal plausibility;
- pharmacological properties of the drug or of the substance class;
- course of the AE after de-challenge and, if applicable, after re-challenge;
- specific tests indicating involvement of the drug in the occurrence/worsening of the AE;
- alternative explanations.

18.7. ADVERSE EVENT RECORDING

Each AE occurring to a subject, either spontaneously revealed by the subject or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the IMP, must be recorded by the Investigator on the AE information page of the eCRF. Also, for SAEs, information must be recorded in the eCRF (see Section 19.1).

The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF and on the “Serious Adverse Event Form” (if appropriate).

18.8. ADVERSE EVENT MONITORING WINDOW

- Start of monitoring: from immediately after the signature of the informed consent
- End of monitoring: final study visit/ETV (observation window)

An AE occurring after the final visit/ETV and coming to knowledge of the investigator (e.g. during a follow-up assessment or by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator’s judgment.

18.9. ADVERSE EVENT REPORTING

The Investigator must report to the CRO all AEs which occur during the trial, regardless of their relationship to IMP. All AEs are recorded by the Investigator on the AE information page of the eCRF.

In addition, any SAE will have to be reported according to the following detailed procedure.

18.9.1. REPORTING SERIOUS ADVERSE EVENTS

Investigators must report SAEs **within 24 hours of first awareness of the event**.

The SAE must be reported through the eCRF to the CRO’s Pharmacovigilance group as per contact details provided in the "List of CRO personnel" at the beginning of this CTP.

If there is any issue with the electronic reporting process, such as internet failure or database issues, this must not delay SAE reporting. The back-up procedure is to send the back-up paper Serious Adverse Event Form to the CRO’s Pharmacovigilance group by email using the contact details specified in the SAE guidelines.

Note: Any reports submitted on paper must be retrospectively added to the eCRF as soon as possible.

The national and local standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

SAEs are reportable from the time a patient signs the informed consent to the follow-up phone call or visit occurring 2 weeks (± 3 days) after the last dose of IMP.

If the Investigator becomes aware of any SAE occurring to a subject within the follow-up window established in this CTP, he/she will report the SAE as above. The SAE will be also reported in the eCRF.

If the Investigator becomes aware of any SAE is related to the study drug outside the follow-up window established in this CTP, it is the Investigator’s responsibility to report the SAE to the Sponsor. The Investigator might use the “Serious Adverse Event Form” via email, but the SAE must not to be reported in the CRF, the SAE is not an event occurred within the trial period.

18.9.2. REPORTING ADVERSE EVENTS OF SPECIAL INTEREST

No specific provisions relate to reporting of AEs of special interest in this trial.

18.10. FOLLOW-UP FOR ADVERSE EVENTS

All AEs requiring the subject's discontinuation and SAEs will be followed up until they are resolved or closed or when the subject is lost to follow up or uncontactable.

Resolution of an AE is defined as the return to pre-treatment status or stabilisation of the condition with the expectation that it will remain chronic.

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) and answer any question that the Sponsor or designee may have regarding the AE.

Regarding SAEs, the timelines and procedure for follow-up reports are the same as those for the initial reports for SAEs.

This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

If follow-up information on SAEs is available, a follow-up information will be filled-in eCRF by the Investigator and sent to the CRO as above-described, under Section 18.9.1.

18.11. PREGNANCY

Subjects must be instructed that known or suspected pregnancy occurring during the trial should be confirmed and reported to the Investigator, who must then withdraw the subject from the trial without delay (Section 10.10). The Investigator should also be notified in case the partner of a male study subject becomes pregnant at any time during the course of the study (in this event a specific ICF for the subject's partner will be obtained).

In the event that a subject or a female partner is found to be pregnant after inclusion in the trial, then pregnancy will be actively followed up to term or pregnancy termination and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the CRO.

The Investigator will send pregnancy reports using pregnancy Reporting and Outcome form to CRO within the timeframes of SAEs.

If pregnancy results in abnormal outcome, it will be considered as SAE. If the Investigator and/or the Sponsor considers this to be due to the IMP, this will be treated as an expedited ADR report.

19. RECORDS

19.1. CASE REPORT FORMS, SOURCE DATA AND QUERY RESOLUTION

The Investigator must ensure that the clinical data required by the CTP are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the official files (source documentation).

Data entered directly into the eCRF comprises all data raised via the 4-point ordinal scales for the assessment of expectoration difficulty, sputum viscosity, sputum color and cough and the 24-hour sputum volume.

ECG and laboratory results must be printed and signed by the Investigator and kept as source data on site after entering outcome into the eCRF.

All other data has to be documented in the subject file as source data first and then entered into the eCRF.

Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a subject visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by trial monitors for completeness and acceptability during monitoring visits.

If data correction is required for an eCRF after initial entry, the site personnel can make necessary corrections on their own or as a response to an automated query by the eCRF system. Monitor and Clinical Data Manager review the eCRF for accuracy and can also generate queries to the investigational staff for resolution.

Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

19.2. RECORDS MAINTAINED BY THE INVESTIGATOR

A copy of all trial records (any documents sent or received from the Sponsor/CRO, correspondence with EC and any other institution or authority and relevant approvals, subjects' source data and subjects' identification documentation) must be maintained by the Investigator for at least 5 years, or for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the Investigator.

19.3. TRIAL MASTER FILE

The Trial Master File (TMF) will be maintained by the CRO according to the respective CRO SOPs with direct access for all study participants.

At the end of the trial, the TMF will be transferred to the Sponsor, where it will be archived according to specific Sponsor SOPs. A copy of the Investigator files will be left on site after trial end.

19.4. TRIAL MONITORING

The trial will be monitored by means of regular visits and telephone calls according to specific and pre-defined SOPs and trial specific monitoring guidelines. Details of the visits will be recorded in appropriate Monitoring Report forms to be submitted regularly to Sponsor. Any relevant protocol deviation must be promptly communicated to designated Sponsor’s personnel

Monitoring will be performed by personnel of the CRO, Parexel.

19.5. CONFIDENTIALITY OF SUBJECT’S INFORMATION

The Investigator has the responsibility to maintain the pseudonymity of subjects in compliance with the Chinese and Italian data protection laws. In all trial documents, subjects are associated to a code which does not reveal subject’s identity. Only at the site, the Investigator holds the subject’s identity on a Subject Identification Log under his/her responsibility. The Investigator will maintain this for the longest period allowed by his/her own institution and, in any case, until further communication from the Sponsor.

The site and the Sponsor shall process personal data of subjects involved in the clinical trial as data controllers and in compliance with the Italian data protection law, each of them in its area of competence and in accordance with the responsibilities provided by GCP, only in relation to the trial performance and for pharmacovigilance purposes.

Any contracted organisation as data processor including Parexel, the local laboratories, and IWRS provider, will act in compliance with the terms and conditions agreed with the Sponsor.

20. BIOMETRICS

20.1. DATA MANAGEMENT

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at Parexel.

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- eCRF and Electronic Data Capture (EDC) system – data capture
- Statistical Analysis System (SAS®) – statistical review and analysis
- Pharmacovigilance safety database

Subject data will be captured in an eCRF system and reviewed by the Clinical Research Associate in order to check CTP adherence and to detect any data inconsistency or discrepancy (data validation step).

Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version current at trial start and which will be maintained during the trial.

Previous and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Actual versions of coding dictionaries used will be stated in the CTR.

The final data file will be transferred to the Sponsor in the agreed format as soon as possible after the trial is completed.

20.2. STUDY END-POINTS

Primary efficacy end-point

Superiority of NAC over placebo in change from baseline to end of 1-week treatment of mean sputum viscosity score or mean expectoration difficulty score.

The study will be declared success if at least one of two components of the primary end-point will show superiority over placebo.

Secondary efficacy end-points

A. Superiority of NAC over placebo

- in change from baseline to day 3 of mean sputum viscosity score OR mean expectoration difficulty score;
- in change from baseline to day 3 and to end of 1-week treatment of individual scores:
  - mean sputum viscosity score
  - mean expectoration difficulty score

- mean sputum color score
- mean cough score

- in change from baseline to day 3 and to end of 1-week treatment of mean sputum volume

B. Non-inferiority of NAC vs. ambroxol in change from baseline to end of 1-week treatment of mean sputum viscosity score or change of mean expectoration difficulty score.

C. Superiority of ambroxol vs. placebo in change from baseline to day 3 and to end of 1-week treatment of
   - mean sputum viscosity score OR mean expectoration difficulty score;
   - mean sputum viscosity score (individual score)
   - mean expectoration difficulty score (individual score)
   - mean sputum color score
   - mean cough score
   - mean sputum volume

Safety end-points

Counts and frequency distributions of:

- All, mild/moderate/severe, non-serious/serious adverse events
- Vital signs
- Laboratory tests
- 12-lead ECG (normal, abnormal clinically non-significant, abnormal clinically significant)

20.3. SAMPLE SIZE

This study has been powered to reach statistical significance for the superiority comparisons of N-acetyl cysteine (NAC) vs. placebo (primary study objective), and for the non-inferiority comparisons of NAC vs. ambroxol hydrochloride (key secondary study objective) in at least one of the two co-primary endpoints at the end of the 1-week treatment. This implies that sample size computation must account for the type I error inflation caused by the multiplicity over the two co-primary endpoints and by the multiplicity over the study targets (superiority and non-inferiority assessments) as well as the logical relationships among the two family of hypotheses with the non-inferiority testable only provided that the superiority contrast, assessed on the same endpoint, is statistical significant. To accomplish this, a multiple-sequence gatekeeping procedure [21] was implemented in a Monte Carlo (MC) study with 1000 runs and with the Bonferroni correction applied to the set of superiority comparisons (first gatekeeper) and the Hochberg correction applied to the set of non-inferiority comparisons (second gatekeeper) in order to control the overall type I family-wise error rate at the one-tailed 0.025 significance level. Details on the adopted gatekeeping strategy are reported further on.

For the superiority tests, and with group sample sizes of 100 patients in placebo group and 100 patients in NAC group, the Monte Carlo study estimated an overall power (“disjunctive” power) close to 93% to reach statistical significance in at least one co-primary end-point. These calculations are based on a one-sided Mann-Whitney test and assuming a minimal clinically relevant difference of 0,35 points between placebo and NAC on a 0-3-point scale, standard deviation equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two end-points equal to 0.31.

For the non-inferiority tests, a sample of 100 patients per each active treatment group ensures sufficient disjunctive power (Monte Carlo disjunctive power = 82%) to detect non-inferiority between NAC and ambroxol in at least one co-primary end-point. These calculations are based on a one-sided non-inferiority t-test assuming a margin of non-inferiority equal to 0.30, standard deviation

equal to 0,79 and 0,77 for sputum viscosity and expectoration difficulty scores (change from baseline to the 1-week treatment) respectively and a correlation between the two endpoints equal to 0.31.

Assuming a drop-out rate of about 10% over one week of entry, a total of 333 patients will be randomized (i.e. 111 patients in the placebo group, 111 patients in the NAC group and 111 patients in the ambroxol group. The sample size calculations were performed using the Mediana package [22].

20.4. STATISTICAL ANALYSES

20.4.1. GENERAL STATISTICAL CONSIDERATIONS

All data captured on eCRFs will be available as listings.

The statistical analysis will be performed by the CRO and it will be carried out according to ICH guidelines ICH E9: “Statistical Principles for Clinical Trials” (CPMP/ICH/363/96). If not otherwise stated all statistical analyses and data tabulations will be produced using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA).

The data from all sites will be pooled. Unless stated otherwise, all available data from withdrawn subjects will be included in the analysis up to the time of withdrawal.

The primary study objective will be assessed by testing superiority of NAC compared to placebo and will be achieved if at least one of the two co-primary end-points will be found statistically significant. The key secondary objective will be assessed through the analysis of non-inferiority of NAC compared to ambroxol and, similarly, will be reached if at least one of the two co-primary end-points will be found statistically significant. Conversely, the analyses on the remaining secondary efficacy endpoints will be treated as non-key secondary objectives since they will be performed only to support primary endpoints findings.

All tests will be one-sided and performed at the significance nominal level of $\alpha = 0.025$. Details are reported in Section 20.4.5.

More detail about the statistical analysis will be provided in the SAP. The SAP will be released before the start of the study. Any change in the SAP occurred after release will be documented as an amendment. Any deviation from the SAP occurring after breaking the blind will be documented and justified in the final CTR and deviations will be clearly marked as ‘post hoc’ analyses.

20.4.2. TRIAL POPULATIONS

There will be 4 analysis populations defined for the trial analyses:

Intention-To-Treat (ITT) Population: The Intention-To-Treat Population will include all subjects who provided informed consent and received a patient number (randomisation number) whether or not they receive IMP.

Modified Intention-To-Treat Population: The Modified ITT (mITT) Population will comprise all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.

Primary analyses will be performed on the mITT population with exclusions from the ITT defined and justified in the SAP.

Following the ITT principle, subjects will be analysed according to the treatment they have been assigned to at randomisation.

The mITT will be used to produce summaries of baseline subject characteristics and for the analysis of all efficacy endpoints.

Safety Population

The Safety Population will comprise all subjects who provide Informed Consent and received at least 1 dose or partial dose of IMP.

Subjects will be analysed according to the treatment they actually received.

The Safety Population will be used to produce summaries of all safety related endpoints and demography.

Per-protocol Population

The Per-protocol Population (PP) will include all mITT subjects who were compliant with study drug administration (i.e. had a compliance of at least 80%) and who had no major protocol deviations that were considered as potentially impacting the efficacy results. Major protocol deviations might include, but are not be limited to, subjects taking a not-permitted concomitant medication, the IMP not being administered during the trial as defined in the protocol, subjects receiving a treatment different than the one assigned by randomisation; others will be defined in the SAP.

With the exclusion of non-inferiority comparisons, results of the primary and secondary efficacy endpoints analyses conducted in the PP will be considered as supportive.

Exclusion of subjects from the PP analyses will be decided jointly by the CRO and Sponsor's Medical Monitor, Clinical Trial Manager and Statistician prior to unblinding of the randomisation code and database release.

The subjects or observations to be excluded, and the reasons for their exclusion will be documented and approved by the above-mentioned persons prior to database release. The documentation will be filed together with the remaining trial documentation.

The number of subjects in each analysis population will be reported. Violations excluding subjects from any particular population will be described, reporting the number of protocol violators per each criterion. All protocol violations, minor ones included, will be listed.

20.4.3. EFFICACY DATA

If not otherwise stated the mITT population will be used for the primary analyses of each of the efficacy endpoints whilst results from supplemental analyses using the Per Protocol Population will be compared to those based on the mITT population to assess the effects of dropouts, missing data and exclusions for protocol violations.

The distributions of all the efficacy endpoints listed in Section 20.2 will be summarized by treatment group and time point. Counts and percentages will be reported with the latest computed based on the numbers of patients with non-missing observations. The percentages will be suppressed when the count is zero in order to draw attention to the non-zero counts. Furthermore, efficacy endpoints will be further summarized by arithmetic means, standard deviations, medians quartiles, minima and maxima.

20.4.3.1. ANALYSIS OF PRIMARY END-POINTS

The co-primary efficacy endpoints are: "the change from baseline to the 1-week treatment in sputum viscosity score" and "the change from baseline to the 1-week treatment in expectoration difficulty score" and will be analyzed on the mITT and PP populations by means of stratified Mann-Whitney U Statistics for testing the hypotheses of superiority of NAC versus placebo (primary objective) after blocking for baseline score and by means of a modified Mann-Whitney U Statistics [23] for testing the hypotheses of non-inferiority of NAC versus ambroxol (key secondary objective) assuming a margin of non-inferiority equal to 0.30. Statistically significant results will be needed on

both mITT and PP populations to accept the hypothesis of non-inferiority of NAC versus ambroxol. Point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

20.4.3.2. ANALYSIS OF SECONDARY ENDPOINTS

- Change from baseline to day 3 in sputum viscosity score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (stratified Mann-Whitney U Statistics blocking for baseline score), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 in expectoration difficulty score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (stratified Mann-Whitney U Statistics blocking for baseline score), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 and to the end of the 1-week treatment period in sputum color score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (stratified Mann-Whitney U Statistics blocking for baseline score), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 and to the end of the 1-week treatment period in cough severity score: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (stratified Mann-Whitney U Statistics blocking for baseline score), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.
- Change from baseline to day 3 and to the end of the 1-week treatment period in sputum volume: the hypothesis of superiority of NAC compared to placebo will be assessed using the same nonparametric test (stratified Mann-Whitney U Statistics blocking for baseline score), whilst point estimates of treatment differences together with associated two-sided 95% confidence intervals will be computed using nonparametric bootstrap.

The same statistical analysis (stratified Mann-Whitney U Statistics blocking for baseline score) will be carried out for testing superiority of ambroxol vs. placebo on the same efficacy endpoints. Results will be used for the purpose of verifying study's assay sensitivity.

20.4.3.3. SUBGROUP ANALYSES

Upon completion of the study, the study statistician in consultation with Zambon's Clinical Team will determine the proportion of concomitant medications between the treatment groups and will decide whether to perform subgroup efficacy analyses if deemed appropriate. The analyses described for the primary and secondary efficacy endpoints will be performed separately for each of the identified stratums.

20.4.4. HANDLING OF MISSING DATA

Missing data on the primary and secondary efficacy endpoints will be imputed as treatment failures (MVTF) by replacing missing values with the scores recorded at baseline or last measurement, whichever is worse as primary imputation method. Expectation-maximization (EM) algorithm and

last observation carried forward (LOCF) will also be used as sensitivity analyses. Details regarding the EM algorithm (i.e. the randomization seed and the SAS code that will be used) will be reported in the SAP.

20.4.5. MULTIPLICITY

The overall type I family-wise error rate will be preserved at the one-tailed 0,025 nominal level (i.e. $\alpha = 0,025$) by controlling multiplicity over the two co-primary endpoints and over the two study targets (superiority and non-inferiority) using a multiple-sequence gatekeeping procedure [20]. To achieve this, the analyses on primary endpoints will be grouped into two family of comparisons (gatekeepers) and processed as follows:

1. The first gatekeeper includes the superiority contrasts “NAC vs placebo” with the adjustment for multiple comparisons across the two co-primary endpoints performed according to Bonferroni. This implies that a difference will be considered statistically significant for a one-tailed p-value ≤ 0.0125 (i.e. $\alpha/2 = 0.0125$). The transition to the second gatekeeper requires that at least one of the two co-primary endpoints is statistically significant.
2. The second gatekeeper includes the family of non-inferiority contrasts “NAC vs ambroxol”. The analyses in the second gatekeeper will be performed depending upon the results obtained in the first gatekeeper as shown below:
    a. If both superiority contrasts will be found statistically significant, non-inferiority will be tested on both co-primary endpoints with an overall probability α set to 0,025 (one-tailed) and with the adjustment for multiple comparisons across the two co-primary endpoints performed according to Hochberg.
    b. If only one of the two superiority contrasts will be found statistically significant, non-inferiority will be tested only for that co-primary endpoint and will be considered achieved if the associated one-tailed p-value will be ≤ 0.0125.

Consistent with the hypothesis testing process performed on the co-primary endpoints, the strategy described above will also be applied to control the coverage of confidence intervals at the two-tailed 95% nominal level (i.e. $1 - 2\alpha = 0,95$).

The analyses on secondary efficacy endpoints (not key) will be performed only to support primary endpoints findings and/or for explorative reasons, therefore no adjustment of significance level will be made to account for multiple comparisons.

20.4.6. MULTICENTER STUDY

As additional analysis, a test of site-by-treatment interaction will be carried-out using a two-way nonparametric ANOVA performed by resorting to the “Aligned Rank Transform” (ART) procedure [24]. The interaction will be considered statistically significant for a two-tailed $\alpha=0.1$. Also, in order to graphically assess the possible heterogeneity of the treatment effect across centres, forest plots will be generated to display the results at each center. In case that the number of patients in each site were scarce, sites will be gathered into “region”. Upon completion of the study and prior to unblinding, study statisticians in consultation with the clinical team will determine the pooling based on enrolment numbers and geographical proximity.

20.4.7. INTERIM ANALYSES

No interim analyses are planned.

20.4.8. SAFETY DATA

All safety endpoints will be summarised and analysed using the Safety Population.

Incidence of Treatment Emergent Adverse Events

The number and the percentage of subjects reporting TEAEs, treatment emergent SAEs, severe TEAEs, TEAEs leading to discontinuation and TEAEs leading to death will be presented by treatment group, along with the number of events occurring.

TEAEs will be summarised also by System Organ Class and Preferred Term according to MedDRA; they will be additionally summarised by severity and relationship to treatment. A separate summary table will be provided for SAEs.

Only TEAEs, i.e. events with an onset date on or after the date of IMP start, will be included in the summary tables. Individual data listings will include all AEs recorded; a separate listing will be provided for treatment-emergent SAEs.

Vital Signs

Descriptive statistics for vital signs will be presented overall and by treatment.

Physical examination data.

Descriptive statistics for physical examination data will be presented overall and by treatment.

Haematology and clinical chemistry

Haematology and clinical chemistry tests results will be converted to standard international units and summarised by treatment group using descriptive statistics for continuous variables. Summaries for change from Visit 1 will be also provided. Frequency of subjects with values appearing outside the central laboratory normal range will be reported by visit for each treatment group. All values appearing outside the laboratory normal range will be highlighted in listings.

12-lead Electrocardiogram

Descriptive statistics for ECG results will be presented overall and by treatment (normal, abnormal clinically non-significant, abnormal clinically significant).

Adherence and Exposure

Subject adherence will be summarised by treatment group presenting descriptive statistics and percentages of adherent subjects, i.e. with a least 80% of compliance.

The total number of doses of IMP taken by each subject, will be summarised as well.

If an AE has a partial or fully missing date, and it is unclear whether the AE is treatment-emergent, it will be assumed that it is. In the AEs analysis, when relationship to study drug is missing for a treatment-emergent adverse event it will be imputed to be drug related. More detail will be provided in the Statistical Analysis Plan (SAP).

21. INFORMED CONSENT

Written informed consent will be obtained by the Investigator or other authorized person from all subjects or their legally acceptable representative.

The Investigator is responsible for correctly obtaining the informed consent in accordance with the applicable regulatory requirement(s), GCP and the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, the Investigator should have received the EC written approval of the ICF.

Informed consent must be obtained prior to the initiation of any procedures specific to the trial. The record of the informed consent must be available to be audited/inspected by the Sponsor/CRO designees and by CA(s), whenever requested.

The informed consent documentation must be personally dated and signed by the trial subjects, to confirm that consent is based on information that has been understood, and by the Investigator.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

Before informed consent may be obtained, the Investigator or other authorised person, should provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject.

The subject should receive a copy of the signed and dated ICF and any other written information provided to him/her, and updates.

If the subject is not able to write, a verbal consent can be obtained. For illiterate patients, at least 1 impartial witness must be invited to join in the consent process, who would sign off ICF.

Further, in case the subject and his/her legal representative are unable to read, informed consent will be obtained in the presence of an impartial witness, i.e. a person independent of the trial who will read the ICF and the written information for the subject.

22. ETHICS COMMITTEE APPROVAL

This trial will be undertaken only after written and dated approval from EC has been received by the Investigator and by the Sponsor for CTP, all its appendices, ICF, and subject's recruitment procedures (i.e. advertisement) if applicable.

In addition to the above-mentioned documents, the EC will be provided with an updated Investigator Brochure, SmPc and IMPD (where applicable), the Investigator's up-to-date Curriculum Vitae and/or other documentation evidencing qualifications, and any other documents that the EC may need to fulfil its responsibilities.

During the trial, on regular basis, the Investigator will have to submit written summaries of the trial status (i.e. recruitment rate) to the EC, if requested.

23. REGULATORY REQUIREMENTS

The trial is to be conducted in compliance with the Chinese legislation and ICH-GCP E6 Rev2.

Selection of subjects will not start prior to the approval of the EC has been obtained and the trial notified to or authorised by CAs as per national and local requirements.

24. QUALITY ASSURANCE

This CTP has been audited by the Sponsor's Quality Assurance. The Audit Plan for the study includes site audits. Audits will be planned and conducted according to the Sponsor's SOPs.

25. INSURANCE

The Sponsor is concerned with the safety of the subjects in the clinical trial and wishes to protect the Investigator (and as applicable per local regulations, the site, the monitor and all the Investigator's staff involved in the trial) in the event of claims or lawsuits alleging injury as a result of administration of a study drug.

In consideration of undertaking a human trial in subjects according to this CTP the Sponsor will:

- indemnify the Investigator and hold him without liability for claims for damages arising out of the above described investigation in excess to those covered by his/her own professional liability insurance;
- defend the Investigator against any claims or lawsuits initiated by, or on behalf of, subjects who seek damages for bodily injury alleged to have been sustained as a result of administration of the study drug;
- pay any settlements of judgement resulting therefrom, providing that for all of the aforementioned cases, the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor;

Indemnification is not valid for claims for damages arising from malpractice and/or negligence on the part of the Investigator or those under the Investigator's supervision.

The protection afforded by this policy does not take the place of the Investigator's professional liability insurance but covers damages in excess of such insurance protection. Further, this indemnity is conditional upon the Investigator giving the Sponsor information as soon as reasonably practicable and upon the Investigator assisting the Sponsor and its authorised representatives in the investigation and defence of any suit for which coverage is provided.

26. CLINICAL TRIAL REPORT

A CTR of the trial will be prepared and written by the CRO according to ICH topic E3 (CPMP/ICH/137/95). A summary of the report will be sent to Investigators/EC/Regulatory Authorities according to current regulations.

27. USE OF INFORMATION AND PUBLICATION

Investigator agrees to inform in advance Zambon about his/her intention to divulge any data, results concerning the Confidential Information and/or the trial subject to this agreement. As a consequence hereof, Investigator hereby undertakes to submit to Zambon, at least with a 60 days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon’s rights to preserve and protect its intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the trial is conducted .

Further, without any prejudice to Investigator’s right to divulge and save for what stated hereinabove, Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the trial hereto.

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29. ANNEX

Annex 1: Diagnostic criteria for the underlying respiratory disease at baseline

30. APPENDICES

Appendix 1: Trial Flow Chart

Appendix 2: SmPC of NAC

Appendix 3: PI of ambroxol hydrochloride

Appendix 4: Investigator Signature Page

Annex 1

Diagnostic criteria for the underlying respiratory disease at baseline

Disease	Main Diagnostic criteria	International/national reference
Acute Bronchitis	Cough (clear, yellowish, purulent) malaise, difficult breathing, and wheezing. The symptoms may have been preceded by upper respiratory infection symptoms of runny nose, sore throat, fever, and malaise	ERS guidelines
Chronic Bronchitis/Emphysema and Acute exacerbations	breathing difficulty, cough, mucus (sputum) production and wheezing	GOLD 2018
Mucoviscidosis	progressive decline of lung function with episodes of acute worsening of respiratory symptoms such as cough, increased sputum production, shortness of breath, chest pain	ECFS guidelines
Bronchiectasis	Cough, tenacious sputum, one or more exacerbations/year, radiographical presence of bronchial wall thickening and airway dilatation on chest computed tomographic (CT) scans.	British Thoracic 2019/Chinese Expert Consensus

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- Chronic Bronchitis/Emphysema and Acute exacerbations https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf
- Mucoviscidosis https://www.cysticfibrosisjournal.com/article/S1569-1993(18)30029-8/fulltext
- Bronchiectasis

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Appendix 1

Trial Flow Chart

ACTIVITIES (See sections 9 & 10 for details)	Visit 1 Screening	Visit 2 Randomisation		Visit 3			Visit 4 End of treatment (EoT)	Follow-up phone call or Visit	Unscheduled deterioration visit	Premature discontinuation visit)
	Within 7 days of Visit 2	Day 1	Day 2	Day 3	Day 4	Day 5 & 6	Day 7	2 weeks ± 3 days after EoT or DV		
Informed consent	X									
Verification of eligibility for randomization	X	X								
Medical history/demography	X									
Pregnancy test		X					X		x	X
Vital signs	X	X		X			X		x	X
Physical examination	X	X		X			X		x	X
Previous/concomitant medications	X	X		X			X	X		X
12-lead ECG	X						X		x	X
Blood sample for haematology and clinical chemistry	X						X			X
Assessment of expectoration difficulty, sputum viscosity, sputum color and cough by means of the 4-point ordinal scales provided		x		x			x		X	X
24-h sputum collection (to be collected and measured the following day)		X		X			X			X
IMP dispensation		X	X	X	X	X	X			
Accountability of IMP		X	X	X	X	X	X		X	X
AE monitoring	X	X		X			X	X	x	X

Appendix 2
Summary of Product Characteristics – N-Acetyl cysteine (NAC)
Switzerland

Fluimucil 10%

Qualitative and quantitative composition

Active ingredient: Acetylcysteine.

Excipients: Sodium edetate, Aqua q.s. to solution.

Pharmaceutical form and quantity of active ingredient per unit

Injection solution for i.v., i.m., local application.

Ampoules: 300 mg acetylcysteine per 3 mL (100 mg/mL).

Therapeutic indications

In respiratory tract diseases that lead to the formation of viscous secretions, which can not be or can only be insufficiently expectorated

Pneumology: All forms of bronchitis, emphysema, atelectasis, bronchiectasis, cystic fibrosis.

ENT diseases: Laryngitis, sinusitis, pharyngitis and laryngectomised patients.

Surgery: Prophylaxis of bronchopulmonary complications with mucostasis.

Paediatrics: Bronchitis, cystic fibrosis.

Intoxications: Antidote for paracetamol intoxications.

Posology and method of administration

Inhalative application

Adults: inhale 1 ampoule 1-2 times a day.

Children of an age where they can actively participate: inhale ½ ampoule 1-2 times a day.

Instillations

Adults

Intraauricular and intranasal: 2-3 drops 2-3 times a day;

Endotracheal: 10-20 drops up to 1 ampoule 1-2 times a day;

Rinsing of other body cavities: ½ ampoule per rinse.

Children

Intraauricular and intranasal: 1-2 drops 1-2 times a day;

Endotracheal: 10 drops up to ½ ampoule 1-2 times a day.

Intravenous use

As a mucolytic in intensive care

Adults: 2-3 ampoules 2-3 times a day.

Children (see «Special dosage instructions»): 1-1½ ampoules 2-3 times a day.

It is recommended to dilute the ampoules with a 0.9% NaCl solution or with a 5% glucose solution and administer the solution slowly as a short infusion (over approx. 5 min.).

Intramuscular use

Adults: 1 ampoule 1-2 times daily by deep i.m. injection.

Children (see «Special dosage instructions»): ½ ampoule 1-2 times daily by deep i.m. injection.

Antidote for paracetamol intoxications

Intravenous dosage schedule according to Prescott

Total dosage: 300 mg/kg acetylcysteine, total duration 20 h.

The following treatment schedule is recommended:

Patients weighing ≥ 20 kg

For this specific use, the 20% concentration ampoules (Fluimucil 20%) are more suitable.

Patients weighing less than 20 kg:

Initial bolus 150 mg/kg in 3 mL/kg solution (over 60 min) followed by 50 mg/kg in 7 mL/kg (over 4 h), followed by 100 mg/kg in 14 mL/kg (over 16 h).

Depending on body weight, the 20% concentration ampoules (Fluimucil 20%) may be more suitable.

A faster initial bolus over 15 minutes may also be administered, but a slower bolus administration (over 60 minutes) reduces the likelihood of anaphylactoid reactions.

Special dosage instructions

Children: In infants and babies under 1 year of age, the product should only be administered under inpatient medical supervision.

In children under 6 years, oral treatment with appropriate dosage forms may be preferable to parenteral treatment.

Contraindications

Hypersensitivity to the active ingredient acetylcysteine or to any of the excipients mentioned in section *composition*.

Special warnings and precautions for use

Intravenous administration of acetylcysteine should be performed under strict medical supervision. Undesirable effects of treatment with acetylcysteine are more likely to occur if

administration is too rapid or excessive. It is therefore recommended that dosage instructions are strictly adhered to.

In patients weighing less than 40 kg, the (antidote)administration should be carefully dosed, because of the potential risk of hypervolemia (fluid overload) which may lead to hyponatremia and seizures. It is therefore recommended that dosage instructions are strictly adhered to.

In cases of direct intravenous administration of high doses (as antidote), pseudo-anaphylactic reactions have been observed occasionally.

For this reason, patients should be monitored and at the onset of the first symptoms, adequate therapeutic measures should be taken.

For aerosol treatment of asthma patients, it is advisable to administer Fluimucil 10% simultaneously with bronchodilators.

Simultaneous administration of an antitussive drug may, by suppressing the cough reflex and physiological self-cleaning of the respiratory tract, result in congestion of the mucus with risk of bronchospasm and respiratory tract infection.

Patients with bronchial asthma should be closely monitored during treatment. If a bronchospasm occurs, acetylcysteine must be discontinued and adequate therapeutic measures taken.

Caution is advised in patients with risk of gastrointestinal bleeding, especially during concomitant administration with other medicinal products inducing irritation of the gastric mucosa.

Administration of acetylcysteine may prolong prothrombin time in addition to paracetamol toxicity.

Information in case of low-sodium diet

Fluimucil 10% contains 43 mg sodium (1.9 mmol) per 3 ml ampoule.

Interactions

There are no *in vivo* interaction studies for the medication.

So far, the reports mentioning an inactivation of antibiotics by acetylcysteine relate exclusively to *in-vitro* studies in which the substances concerned had been directly mixed. Therefore, Fluimucil 10% should not be co-administered with other medicinal products in the same solution (see "Other Information, Incompatibilities").

Since thiol compounds may form addition compounds with naphthoquinones, there is also the theoretical possibility that a reaction with vitamin K may occur. Although it has not been

established whether this can occur *in vivo*, the administration of vitamin K for the treatment of hypoprothrombinemia in liver failure should begin a few hours after the cessation of acetylcysteine administration.

The vasodilatory and the inhibiting thrombocytes aggregation effects may be enhanced by the simultaneous administration of glyceryl trinitrate (nitroglycerin). The clinical importance of these findings has not yet been determined.

If co-treatment with parenteral nitroglycerin and acetylcysteine is considered necessary, the patient should be monitored for potential hypotension, which may be severe and may be indicated by the presence of headache.

Pregnancy/Breast-feeding

Pregnancy

Data from a limited number of exposed pregnant women showed no adverse effects on pregnancy or the health of the foetus or the newborn.

Experience from epidemiological studies is not available.

Animal studies have not indicated any direct or indirect toxicity with any effect on pregnancy, embryonic development, development of the foetus and/or postnatal development.

If used during pregnancy, caution is advised.

Breast-feeding

There are no studies showing whether or not acetylcysteine passes into breast milk.

Effects on ability to drive and use machines

Effects on the ability to drive or operate machinery has not been studied.

Undesirable effects

The most common undesirable effects described in the literature regarding the acetylcysteine administered intravenously are skin rash, urticaria and pruritus, and they most commonly occur during administration of the initial bolus.

In a randomised, open multi-centre study, during the first 2 hours after i.v. administration of acetylcysteine, the following undesirable effects occurred:

Immune system disorders

Very common: anaphylactoid reaction (17%).

Cardiac disorders

Common: Tachycardia.

Respiratory, thoracic and mediastinal disorders Uncommon: Pharyngitis, rhinorrhoea, rhoncus, bronchospasm.

Gastrointestinal disorders

Common: Vomiting (11%), nausea.

Skin and subcutaneous tissue disorders Common: Pruritus, skin rash.

Vascular disorders

Common: Facial flushing.

The following undesirable effects have been reported based on long-term post-marketing experience and their frequency can not be estimated from the available data.

Local administration

Immune system disorders: Hypersensitivity reaction.

Respiratory, thoracic and mediastinal disorders: Bronchospasm, rhinorrhoea.

Gastrointestinal disorders: Stomatitis, vomiting, nausea.

Skin and subcutaneous tissue disorders: Angioedema, urticaria, rash, itching.

Systemic administration (high dose i.v. administration)

Immune system disorders: Anaphylactic shock, anaphylactic/anaphylactoid reactions, hypersensitivity reaction.

Cardiac disorders: Tachycardia.

Respiratory, thoracic and mediastinal disorders: Bronchospasm, dyspnoea.

Gastrointestinal disorders: Vomiting, nausea.

Skin and subcutaneous tissue disorders: Angioedema, urticaria, facial flushing, rash, itching.

General disorders and administration site conditions: Face oedema.

Investigations: blood pressure decreased, prothrombin time prolonged.

The occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome has been very rarely reported in temporal relation to the use of acetylcysteine. In case of new manifestations of cutaneous and mucosal manifestations, a doctor should be consulted immediately and the use of acetylcysteine should be discontinued. In most of these reported cases, at least one other drug had been used and possibly enhanced the observed mucocutaneous effects.

Different studies confirm the decrease in Platelet aggregation when using acetylcysteine. The clinical significance of this is still unknown.

Overdose

Intravenous administration

Symptoms of overdose with intravenous administration are similar to adverse effects, but more pronounced.

In case of overdose, discontinue the infusion and initiate symptomatic treatment.

There is no specific antidote treatment. Acetylcysteine is dialysable.

Local administration

No cases of overdose have been reported with local administration.

Pharmacodynamic properties

ATC-code: R05CB01

Mechanism of action and pharmacodynamic properties

Fluimucil 10% contains the active ingredient acetylcysteine, a cysteine derivative with a free SH group that has both mucolytic and antioxidant properties.

The mucolytic effect of acetylcysteine relies on the ability of the SH group to reduce the disulphide bridges of the mucoproteins of the mucus.

The antioxidant property of Fluimucil 10% is based on the fact that electrophilic and oxidative compounds are directly inactivated by acetylcysteine and indirectly via glutathione. Electrophilic compounds are inactivated by conjugation, and oxidizing compounds are neutralized by reduction.

Acetylcysteine provides an essential precursor to glutathione synthesis through cysteine, increasing endogenous glutathione levels.

Glutathione is an important nucleophilic and antioxidant mechanism of action of the organism and is therefore of great importance for its protection. Glutathione may also inactivate the toxic, reactive, electrophilic metabolites produced in certain intoxications (e.g., paracetamol intoxication) by forming inert complexes.

Fluimucil 10% does not affect the body's immune defenses nor the ciliary function of the respiratory tract and does not cause dissolution of fibrin or blood clots.

Clinical efficacy

Fluimucil 10% dissolves the viscous mucus in the airways, promotes expectoration and helps allay the coughing stimulus. This facilitates breathing.

Other clinical parameters that may be positively influenced by Fluimucil 10% include dyspnoea and lung function.

When used as an antidote for paracetamol intoxications, Fluimucil 10% works by restoring the glutathione level in hepatocytes or, in its place, as an alternative substrate promoting the conjugation of toxic metabolites of paracetamol.

Pharmacokinetic properties

Following i.v. administration, acetylcysteine diffuses rapidly in the body, mainly in the aqueous medium of the extracellular space and reaches the highest concentrations in the liver, kidneys, lungs and bronchial mucus.

In the body, acetylcysteine is found either in free form or reversibly plasma protein bound by disulfide bridges.

Following i.v. dosage of 200 mg of acetylcysteine the following pharmacokinetic data was obtained.

The maximum plasma concentration of total acetylcysteine (free and bound) was 120 µmol/L, for the free form it was 75 µmol/l.

The volume of distribution was 0.47 L/kg (free and bound), or 0.59 L/kg (free form). Total clearance was determined as 0.11 L/h/kg (total) and 0.84 L/h/kg (free). Elimination half-life was approx. 5.6 h, and for the free form approx. 2 h.

In newborns or patients with severe hepatic insufficiency, a prolonged elimination half-life is to be expected.

Elimination

About 30% of the administered dose is eliminated directly by the kidneys. The main metabolites are cystine and cysteine. In addition, small amounts of taurine and sulphates are excreted.

No studies are available on the excretion of the portion not eliminated through the kidneys.

Preclinical safety data

Mutagenic effects of acetylcysteine are not expected. A test on bacterial organisms was negative. Studies on the tumorigenic potential of acetylcysteine were not carried out.

Embryotoxicity studies have been conducted in pregnant rabbits and rats, to which a dose of oral acetylcysteine has been administered during the gestation period. None of these experimental studies revealed fetal malformations. Fertility, peri- and postnatal development studies were performed in rats with oral acetylcysteine. The results of these studies demonstrate that acetylcysteine does not affect gonadal function, fertility, infants, or the development of newborn animals.

Other information

Incompatibilities

Acetylcysteine is incompatible with most metals and is inactivated by oxidising substances. Therefore, if possible, containers made of glass or plastic (but not rubber) should be used for administration.

Fluimucil 10% should not be co-administered with other medicinal products, in particular antibiotics, in a single solution or within the same container.

Influence on diagnostic methods

Acetylcysteine may affect the colourimetric assay of salicylates.

In urinalysis, acetylcysteine may affect the results when determining ketone bodies.

Shelf life

Unopened ampoules may not be used after the date stated on the container after "Exp".

If the ampoule has been opened, discard any unused solution.

Special precautions for storage

Store at room temperature (15-25 °C) in the original packaging, in order to protect from light, and keep out of the sight and reach of children.

Instructions for use

Instruction for opening the ampoule

- Keep the ampoule in the correct position (i.e., with the marked point upwards) (Figure 1)
- Apply pressure with the thumb above the point and break the ampoule head away (Figure 2)

I.V. administration

Fluimucil 10% is compatible with the following solutions for infusion: 5% glucose solution and 0.9% NaCl solution. The diluted infusion preparation is not preserved. It is chemically and physically stable for 24 hours at room temperature.

However, for microbiological reasons, the ready-to-use preparation should be used immediately after dilution. Any remaining solution must be discarded.

Aerosol therapy

For aerosol use, administration should be performed using an inhalation device. Dilution of the ampoule is not necessary, yet is possible (e.g., 1 ampoule of Fluimucil 10% (3 mL) + 7 mL of 0.9% NaCl solution to reach a final volume of 10 mL).

The use of equipment with glass or plastic parts is preferable.

If equipment with metal or rubber parts is used, rinse immediately with water after use.

Marketing authorisation number

66860 (Swissmedic).

Packaging

Fluimucil 10% solution for injection ampoule 5 × 3 mL. (B)

Marketing authorisation holder

Zambon Switzerland AG, 6814 Cadempino.

Date of information

May 2012

Appendix 3
Package Insert – Ambroxol hydrochloride
China

[Drug Name]

Generic name: Ambroxal Hydrochloride Injection

English name: Ambroxal Hydrochloride Injection

Trade name: Mucosolvan

[Composition]

Ambroxol hydrochloride (also known as bromocyclohexylaminealcohol hydrochloride)

Excipients: Citric acid monohydrate, sodium hydrogen phosphate dihydrate, sodium chloride, water for injection, nitrogen.

[Description]

Colorless clear liquid.

[Indication]

1. Indicated for expectorant therapy in the following patients with acute and chronic respiratory diseases accompanied by abnormal sputum secretion and poor expectoration, such as acute exacerbation of chronic bronchitis, asthmatic bronchitis, bronchiectasis, bronchial asthma and pneumonia.
2. Prophylactic treatment of postoperative pulmonary complications.
3. Treatment of infant respiratory distress syndrome (IRDS) in premature infants and newborns.

[Dosage and Administration]

Adults and children above the age of 12 years: 2-3 times a day, 15 mg each time, slow intravenous injection; the dose can be increased to 30 mg each time for severe cases.

Children aged 6-12 years: 2-3 times a day, 15 mg each time.

Children aged 2-6 years: 3 times a day, 7.5 mg each time.

Children below the age of 2 years: 2 times a day, 7.5 mg each time.

All for slow intravenous injection.

Or add the drug to glucose injection (or normal saline) for intravenous drip.

Treatment of infant respiratory distress syndrome (IRDS): The total daily dose is calculated based on the infant's weight, 30 mg/kg, divided into 4 injections per day. An infusomat should be used for administration, and the duration of intravenous injection should be at least 5 minutes.

[Dosage Form]

Injection

[Adverse Reactions]

The product is well tolerated, and mild upper gastrointestinal adverse reactions have been occasionally reported, mainly including stomach burning, indigestion and occasional nausea and vomiting, occurring mostly after parenteral administration. Allergic reactions are rare, mainly including rash. Few cases have reported severe acute allergic reactions, but the correlation with ambroxol hydrochloride is not yet known, and such patients are often allergic to other substances.

[Contraindication]

Those who are known to be allergic to ambroxol hydrochloride or other ingredients shall not use the product.

[Precautions]

1. Pregnant and breastfeeding women should use the product with caution.

2. It is prohibited to mix the product with other solutions having a pH greater than 6.3, as the increase in pH will lead to free base precipitation of ambroxol.

[Ingredient]

Ambroxol hydrochloride

[**Use in Pregnant and Breastfeeding Women**]

Pre-clinical trials and a great deal of clinical experience in women after pregnancy for 28 weeks have shown that the product has no adverse effect on pregnancy. However, during pregnancy, especially in the first three months of pregnancy, the drug should be used with caution. The drug may enter breast milk, but is supposed to have no effect on infants at the therapeutic dose.

[Pediatric Use]

Keep observing during medication.

[Geriatric Use]

The safety and efficacy of medication in the elderly and young patients have been assessed, and the results have shown no difference.

[Drug Interactions]

Co-administration of the product and antibiotics (amoxicillin, cefuroxime, erythromycin, doxycycline) may increase the concentration of antibiotics in the lung tissue. There has been no report on relevant clinical adverse reactions when the product is used in combination with other drugs.

[Pharmacological Action]

The product is a mucolytic agent, which can increase respiratory mucosal serous gland secretion, and reduce mucus gland secretion, thereby reducing the viscosity of sputum; it can also promote the

secretion of pulmonary surfactants, and increase bronchial cilia movement, so that sputum can easily be coughed up.

[Manufacturer]
Boehringer Ingelheim Shanghai Pharmaceutical Co., Ltd.

Appendix 4: Investigator Signature Page

I have read the attached protocol: **Intravenous NAC Phase III China Trial.** A phase III, multi-centre, randomized, rater- and patient-blind, placebo- and active-controlled, parallel group clinical trial to compare the efficacy and safety of 1-week treatment of intravenous N-acetylcysteine (NAC) 600 mg twice daily (active test treatment), ambroxol hydrochloride 30 mg twice daily (active control treatment) and placebo as expectorant therapies in adult Chinese patients with abnormal sputum viscosity and poor expectoration

I agree to comply with the current International Council for Harmonisation Guidelines for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved.

I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred or if any proceeding for debarment is pending or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the EC.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

PPD

_____

(Printed Name)