NAME OF COMPANY: HEXAL AG	NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP): Acetylcysteine 600 mg effervescent tablet	NAME OF ACTIVE INGREDIENT: acetylcysteine
	For adolescents (≥14 - <18 years): own subject informed consent/ assent to participate in the trial and the informed consent from all parent(s)/ legal guardian(s) provided in written form	
	Exclusion/ Withdrawal Criteria [1] History of hypersensitivity or intolerance to the active substance or any of the excipients of the trial medication [2] Patient with history of hereditary fructose intolerance, galactose intolerance, lactase deficiency or glucose-galactose malabsorption [3] Chronic rhinosinusitis (symptoms lasting longer than 3 months) [4] Subjects who have undergone sinus or nasal surgery for chronic rhinosinusitis in the 6 months prior to screening visit [5] Sinus lavage within 7 days prior to screening visit [6] Odontogenic rhinosinusitis [7] Allergic (perennial or seasonal) rhinitis [8] Bronchial asthma or chronic obstructive pulmonary disease [9] Nasal polyposis or clinically relevant nasal septum deviation [10] Concomitant otitis [11] Intranasal or systemic use of corticosteroids within 30 days prior to screening visit [12] Intranasal or systemic use of antibiotics within 30 days prior to screening visit [13] Use of nasal decongestants within 2 days prior to screening visit [14] Concomitant treatment of common cold-like symptoms within 7 days prior to screening visit with any of the following: a) Analgesics b) Non-steroidal anti-inflammatory drugs c) Antihistamines [15] Concomitant use of intranasal saline irrigation [16] Use of immunosuppressive agents within 30 days prior to screening visit [17] Immunocompromised state [18] Suspicion for acute bacterial rhinosinusitis (defined as presence of purulence for 3 to 4 days with fever ≥ 38.3°C) [19] Pregnant or breast-feeding female patient [20] Female patient of childbearing potential (not surgically sterilized/ hysterectomized or postmenopausal for at least 1 year) who is not currently using (documented at screening visit) and not willing to use medically reliable methods of contraception for the entire trial duration such as oral, injectable or implantable contraceptives, intrauterine contraceptive devices (IUD), sexual abstinence or vasectomized partner [21] Any other condition of the patient (e.g. serious or unstable medical or psychological condition, acute psychosis) that in the opinion of the investigator may compromise evaluation of the trial treatment or may jeopardize patient's safety, compliance or adherence to protocol requirements [22] Participation in ANY research study involving another investigational medicinal product (IMP) within 30 days prior to screening visit, *or* simultaneous participation in another clinical study *or* previous participation in present study [23] Suspected alcohol/ drug dependence or abuse (including heavy	

2.2 Planned Assessments

Type of Assessment planned	VISIT 1 Day -1* SCREENING	VISIT 2 Day 1 RANDOMIZATION	VISIT 3 Day 4	VISIT 4 Day 7	VISIT 5 Day 10	VISIT 6 Day 15 (+3)†	FOLLOW-UP Phone Call within 7 days after Visit 6 (or earlier in case of premature termination)
Informed consent	●						
Demography	●						
Life style, habits	●						
Additional anamnestic information (last participation in any clinical trial, last administration of any investigational drug, allergy/ perennial or seasonal rhinitis, drug hypersensitivity or intolerance)	●						
Specific history (anamnesis) of acute rhinosinusitis	●						
MSS by Patient transcribed from TSSF into the CRF	●	●				●	
Check of MSS documentation in the patient diary‡			●	●	●	●	
SNOT-22 questionnaire by Patient (documented in the diary)		● (Day 1)		● (Day 7)		● (Day 14)	
Medical and surgical history (concomitant/ previous diseases and medications inclusive any treatment of rhinosinusitis, medical and other therapeutic measures)	●						
Changes of concomitant diseases/ medications and medical and other therapeutic measures		●	●	●	●	●	
Contraceptive method used by female patient	●						

* presence of symptoms ≤3 days prior to Visit 1 (screening)
† **End of Treatment on Day 14, but in case of delayed final visit (Visit 6) the patient can voluntarily take reserve study medication for a maximum of 3 additional days**
‡ **MSS in the patient diary once a day before the intake of the morning dose, starting with Day 2 until Day 14** (end of treatment or earlier in case of drop-out) and for a maximum of 3 additional days

Type of Assessment planned	VISIT 1 Day -1* SCREENING	VISIT 2 Day 1 RANDOMIZATION	VISIT 3 Day 4	VISIT 4 Day 7	VISIT 5 Day 10	VISIT 6 Day 15 (+3)†	FOLLOW-UP Phone Call within 7 days after Visit 6 (or earlier in case of premature termination)
Vital signs (blood pressure, pulse rate, body temperature)	●	●	●	●	●	●	
Physical examination per body system; general/ nutritional state	●					●	
Examination of nose, ears, mouth/throat (ENT)	●			●		●	
Safety laboratory examination of blood (hematology, blood chemistry)	●					●	
Serum pregnancy test (hCG) in all female patients	●					●	
Inclusion criteria	●	●					
Exclusion criteria	●	●	●	●	●		
RANDOMIZATION to double-blind treatment		●					
Dispensation of blinded medication		●					
Return and check of used blinded medication			●	●	●	●	
Dispensation of patient diary		●					
Return and check of patient diary			●	●	●	●	
Check of further patient eligibility		●	●	●	●		
Assessment of overall response to treatment by investigator			●	●	●	●	
Overall assessment of tolerability by patient				●		●	
Overall assessment of tolerability by investigator				●		●	
Adverse event questioning		●	●	●	●	●	●

5 Ethical and Legal Aspects of the Conduct of the Trial

This trial will be conducted in accordance with the following:

- Declaration of Helsinki (1964) in the current amended version[2]
- ICH Topic E 6. GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) Step 5 (EMA/CHMP/ICH/135/1995)[3]
- ICH Topic E 8. Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)[4]
- ICH Topic E 9. Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)[5]
- ICH Topic E 3. Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95)[6]
- Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001[7]
- Directive 2005/28/EC of the European Parliament and the Council of 8 April 2005[8]
- Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (2010/C 82/01)[9]
- Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01)[10]
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)[11]
- Drug laws and regulations in the countries of the clinical centers involved
- [redacted] standard operating procedures (SOPs).

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Prior to the initiation of the trial, the protocol, the appropriate information about the active compound (e.g. investigator's brochure or summary of product characteristics [SmPC]), the subject insurance cover, the curriculum vitae of the principal investigator(s), the subject information leaflet, the informed consent/ assent, and the CRF will be submitted to the IEC/IRB responsible for the principal investigator in the country of clinical center(s) for review and approval.

The trial will only be performed when a full approval of this protocol has been obtained from the IEC/IRB in the country of the clinical center(s).

Following approval by the IEC/IRB and regulatory authority (section 5.2) the trial can be initiated immediately after a copy of the ethics vote and the authority approval has been sent to the sponsor/its representative. A list of the members of the IEC/IRB will be attached to the copy of the approval.

8 Investigational Plan

8.1 Overall Trial Design

The trial will be conducted as a prospective, randomized, multinational, multicenter, double-blind study in 4 parallel groups of patients.

Approximately 900 patients with acute, uncomplicated rhinosinusitis will be randomized.

8.2 Discussion of the Trial Design and Rationale

The test product (Acetylcysteine 600 mg effervescent tablet) is registered in many EU as well as non-EU countries for the secretolytic therapy in acute and chronic bronchopulmonary diseases.

The primary aim of this trial is to assess the efficacy of three different total daily doses of the investigational product containing 600 mg acetylcysteine per effervescent tablet compared to placebo for the treatment of acute uncomplicated rhinosinusitis.

The **trial design** was chosen according to the recommendation of the current guidelines EMA/CHMP/ICH/135/1995[3] and CPMP/ICH/291/95[4].

Choice of a double-blind design: Such design has been selected as the blinding of the study personnel and patients is important to reduce any risk of the bias in trial where the outcome efficacy and safety assessments of investigator/ patient can be affected by the type of the IMP administered.

Male and female subjects (patients) with the diagnose of acute, uncomplicated rhinosinusitis defined by the investigator at screening (Visit 1) as *a)* major symptom score (MSS) assessed by the patient ≥8 and ≤12 points[21, 22] for the following: rhinorrhea/ anterior discharge, postnasal drip, nasal congestion, headache, and facial pain/pressure, whereupon the nasal congestion is mandatory and no more than 3 of the 5 symptoms are rated as severe; *b)* individual score for facial pain/pressure ≥1 (mild) and ≤2 (moderate), and *c)* presence of symptoms ≤3 days prior to inclusion will be enrolled in the present trial.

Choice of duration of treatment: Taking into consideration that a randomized, placebo-controlled trial investigating the clinical efficacy of a dry extract of five herbal drugs (BNO 1060) in acute viral rhinosinusitis (Jund et al., 2015)[1] showed statistically significant and clinically relevant improvements in symptoms by end of treatment (14 days) compared to placebo, a 2 weeks treatment phase was chosen for the current trial.

The assessment of efficacy and safety of the treatments will be performed before the first dose and after 3, 6, 9, and 14 days of treatment.

Choice of endpoints: For evaluation of efficacy, the disease activity will be assessed by the defined Major Symptom Score (MSS) and Sino-Nasal Outcome Test (SNOT-22) questionnaire and based on the clinical evaluation of patient-reported relief of symptoms before and during the treatment.

The primary endpoint corresponds to improvements of the clinical condition as defined by the decrease in MSS. Safety will be based on all information available on patient's reports of AEs, vital signs, clinical findings and ENT examination, and overall assessment of tolerability. Adverse events will be recorded by the investigator at each visit until the follow-up phone call (within 7 days after Visit 6, or earlier in case of premature termination).

Safety of higher doses of N-acetylcysteine (NAC):

Not only the NAC doses proposed in this study (up to 1200 mg per intake and up to 2400 mg as total daily dose), but also higher single and/or daily doses have been used in a number of controlled studies in patients with chronic bronchitis and for numerous other indications.

These indications, for example, include other pathologies involving the pulmonary system, such as idiopathic pulmonary fibrosis (Meyer et al. 1994 [23], Demedts et al. 2005[24]) or fibrosing alveolitis (Behr et al. 1997[25]), from which a similar safety profile can be derived as with lower oral daily doses.

As an outcome of a meta-analysis reported by Cazzola et al. (2015)[26] the authors concluded that in COPD with an objective confirmation of airway obstruction, NAC should be administered at a dose of ≥1200 mg per day to prevent exacerbations.

Further evidence for the safety of doses of 1200 mg twice daily can be derived from the use of NAC in the treatment of other non-airway-related pathologies:

- **Paracetamol poisoning**

In paracetamol poisoning, NAC has been regularly administered in doses far beyond 2400 mg per day. The standard antidote for acetaminophen toxicity has been oral NAC with a loading dose of 140 mg/kg, followed by 17 doses of 70 mg/kg every 4 hours (Smilkstein et al. 1988[27]). This corresponds to a daily dose of 39200 mg for 70 kg of body weight.

- **Contrast-induced nephropathy (CIN)**

Richter et al.[28] recently presented an overview of 17 clinical studies on the use of NAC for CIN in more than 2000 patients. The study medication ranged mostly from 600 mg b.i.d. to 1500 mg b.i.d orally administered. The authors concluded that the low incidence of adverse events associated with NAC forms the basis of its recommendation in the guidelines (Richter and Crannage 2015[28]). This conclusion is likewise supported by a similar systematic review and meta-analysis by Kang et al. (2015)[29], who analyzed 20 randomized controlled studies involving 3466 subjects (1756 assigned to NAC). Subjects received either 2400 mg/d p.o. or 2400 ± 2000 mg while in one of the studies the dose was even 10000 mg. In CIN the cumulative NAC doses and routes of administration may also reach 6000 mg p.o. as reviewed by Trivedi et al. (2009)[30]. These authors suggested that in patients at risk of CIN, it is prudent to prescribe NAC 1200 mg orally twice per day for 48 hours without raising any safety concerns.

- **Neuropsychiatric disorders**

In a comprehensive review, Deepmala et al. (2015)[31] analyzed the state of scientific knowledge for the use of NAC in treating psychiatric and neurological disorders. A total of 65 publications met the inclusion and exclusion criteria for the systematic review.

8.4 Selection of Trial Population

8.4.1 Inclusion Criteria

Only patients fulfilling all of the following criteria should be randomized in the present trial:

[1] Male or female subjects aged between 14 and 75 years inclusive on the date of consent

[2] Diagnosis of acute, uncomplicated rhinosinusitis defined at screening Visit 1 and at Visit 2 as:

a) major symptom score (MSS) assessed by the patient ≥8 and ≤12 points for the following: rhinorrhea/ anterior discharge, postnasal drip, nasal congestion, headache, and facial pain/pressure, whereupon the nasal congestion is mandatory and no more than 3 of the 5 symptoms are rated as severe

b) individual score for facial pain/pressure ≥1 (mild) and ≤2 (moderate)

c) presence of symptoms ≤3 days prior to screening visit

[3] For adults (≥18 years): Informed consent to participate in the trial provided in written form; For adolescents (≥14 - <18 years): own subject informed consent/ assent to participate in the trial and the informed consent from all parent(s)/ legal guardian(s) provided in written form.

8.4.2 Exclusion/ Withdrawal* Criteria

Patients presenting with any of the following criteria will not be included in the trial:

[1] History of hypersensitivity or intolerance to the active substance or any of the excipients of the trial medication

[2] Patient with history of hereditary fructose intolerance, galactose intolerance, lactase deficiency or glucose-galactose malabsorption

[3] Chronic rhinosinusitis (symptoms lasting longer than 3 months)

[4] Subjects who have undergone sinus or nasal surgery for chronic rhinosinusitis in the 6 months prior to screening visit

[5] Sinus lavage within 7 days prior to screening visit

[6] Odontogenic rhinosinusitis

[7] Allergic (perennial or seasonal) rhinitis

[8] Bronchial asthma or chronic obstructive pulmonary disease

[9] Nasal polyposis or clinically relevant nasal septum deviation

[10] Concomitant otitis

[11] Intranasal or systemic use of corticosteroids within 30 days prior to

* Withdrawal criteria: exclusion criteria registered starting with Day 1 (Visit 2) and thereafter. Additional withdrawal conditions are specified in protocol section 9.4.1.

- Use of nasal decongestants within 2 days prior to screening visit and during the trial;
- Concomitant treatment within 7 days prior to screening visit of common cold-like symptoms with any of the following:
  - Analgesics
  - Non-steroidal anti-inflammatory drugs
  - Antihistamines
- Concomitant use of intranasal saline irrigation;
- Use of immunosuppressive agents within 30 days prior to screening visit and during the trial.

The following **concomitant therapeutic measures available at home are NOT ALLOWED for the present trial**:

- Infrared light, hot and/or warm pads/compresses, and home remedies, e.g. fragrance lamps with essential oils like rosemary, thyme eucalyptus and mint oil etc.

The following **concomitant medication IS ALLOWED for the present trial**:

- Any other long-term therapy for any chronic disease (if expected to be maintained stable during the entire trial duration).

- **Sino-Nasal Outcome Test (SNOT-22) questionnaire**

SNOT-22 will be assessed by the patient in the patient diary on Day 1, Day 7 and Day 14.

SNOT-22 will be part of the patient diary printed on no-carbon copy paper (one top page and a second no-carbon copy page). The patient must complete the first SNOT-22 in the patient diary during Visit 2, after the investigator explained unclear terms and answered all patient's questions.

The following trial specific efficacy assessments will be performed and documented by the INVESTIGATOR:

- **Investigator's assessment of the overall response to treatment**

The investigator will assess the overall response to treatment at each visit after baseline: on days 4 (Visit 3), 7 (Visit 4), 10 (Visit 5), and 15 (Visit 6).

The investigator will rate the response to treatment using a five-point rating scale: ① = major deterioration, ② = minor deterioration, ③ = no change, ④ = minor improvement, ⑤ = major improvement.

9.2 Trial Specific Safety Assessments

Overall assessment of tolerability by the patient and by the investigator on days 7 (Visit 4) and Day 15 (Visit 6).

- **Patient's assessment of the overall tolerability**

The patient will assess the overall tolerability during the visit on days 7 (Visit 4) and 15 (Visit 6).

The patient will rate the tolerability using a five-point rating scale: ① = very poor, ② = poor, ③ = medium, ④ = good, ⑤ = very good. The investigator will document the patient assessment of overall tolerability in the CRF.

- **Investigator's assessment of the overall tolerability**

The investigator will assess the overall tolerability on days 7 (Visit 4) and 15 (Visit 6).

The investigator will rate the tolerability using a five-point rating scale: ① = very poor, ② = poor, ③ = medium, ④ = good, ⑤ = very good.

Adverse Events (AEs) and Serious Adverse Events (SAEs): AEs will be recorded by the investigator at each visit until the end of the double-blind phase inclusive the follow-up phone call (within 7 days after Visit 6 or earlier in case of premature termination). AEs will be assessed for seriousness, severity and drug-event relationship (details are provided in section 9.3).

Vital signs: Blood pressure, pulse rate, and body temperature will be recorded at each visit: at screening (Visit 1), immediately before randomization (Visit 2; this will constitute the baseline value), and on days 4 (Visit 3), 7 (Visit 4), 10 (Visit 5), and 15 (Visit 6).

ENT examination of **nose** (septum, mucosa, secretion, obstruction, polyps); **ears** (effusion and erythema), **mouth/ throat** (anterior and posterior discharge, dental abnormalities and halitosis) will be recorded at screening (Visit 1), on Day 7 (Visit 4) and on Day 15 (Visit 6).

Safety laboratory examination of blood at screening (Visit 1) and end of treatment (Visit 6) for the following:

Hematology: hemoglobin, hematocrit, leukocytes with differential count, erythrocytes, erythrocyte sedimentation rate, MCV, MCH, MCHC, and platelet count

Blood chemistry:

Electrolytes	sodium, potassium, serum calcium, serum albumin, chloride
Substrates	creatinine, total protein, total bilirubin, blood glucose, urea, uric acid
Enzymes	ALT, AST, γ-GT, ALP

Pregnancy test: In all women a serum pregnancy test for measurement of human chorionic gonadotropin (hCG) will be performed at screening (Visit 1) and at Visit 6.

9.3 Adverse Events

9.3.1 Definitions

An **Adverse Event / Experience (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization
- results in persistent or significant disability/ incapacity
- is a congenital anomaly/ birth defect
- is medically significant: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject (patient) or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

A **(Serious) Adverse Drug Reaction ((S)ADR) is** any (S)AE for which the investigator or sponsor assess a reasonable possibility for a causal relationship to a medicinal product, see 9.3.3 below.

A (Serious) Unexpected Adverse Reactions is defined as a (serious) adverse drug reaction, the nature or severity of which is not consistent with the Reference Safety Information (SmPC).

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Information about common side effects already known about the Investigational Medicinal Product (IMP) can be found in the Reference Safety Information (SmPC) or will be communicated in the form of Investigator Notifications. This information will be included in the subject information and should be discussed with the subject.

For further details, please refer to the Quick Reference Guide for completing the Serious Adverse Event Form.

9.3.2 Severity of Adverse Events

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. In the course of the trial, the investigator will determine whether any AE have occurred and will grade their severity as follows:

- Mild — Usually transient in nature and generally not interfering with normal activities
- Moderate — Sufficiently discomforting to interfere with normal activities
- Severe — Prevents normal activities

9.3.3 Relationship to the IMP

The investigator should evaluate all AEs considering all accessible data, at any time new information becomes available. The definition of IMP includes the test product under evaluation or the placebo that is given during any phase of the trial.

The investigator should assess whether or not, in his/her expert opinion, the AE is suspected to the drug. Suspected means that a causal relationship between the drug and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Causality assessments are critical and must be provided for each unique AE in relation to each IMP, non-investigational medicinal product (NIMP) or other concomitant medication, if applicable. Missing causality assessments will be handled as suspected to IMP by the sponsor.

AEs with a suspected relationship to NIMP or other concomitant medication (for both Sandoz and non-Sandoz products), even if non-serious, need to be reported by the investigator to the respective Country Patient Safety Head (see section 9.3.5 for contact details).

9.3.4 Adverse Events Documentation

Any AE (non-serious and serious) occurring after the subject has provided study-specific informed consent and until the last study visit of the subject, has to be recorded on the AE pages of the Case Report Form (CRF).

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. AEs also may be identified when they are volunteered by the subject during or between visits or during physical examination, laboratory test or other assessments. All AEs should be given appropriate medical care. Treatment may include one or more of the following: no action taken (i.e. further observation only); IMP dosage adjusted/temporarily interrupted; IMP permanently discontinued due to this AE; concomitant medication given; non-drug therapy given, patient hospitalized / patient's hospitalization prolonged. The treatment of the AE should be documented in the CRF. In addition, the action taken with the IMP should be documented, and should be assigned to one of the following categories: not changed, withdrawn, reduced, increased, interrupted, unknown and not applicable.

Concomitant medication, other treatments or changes in the administration of the IMP should be specified and documented.

Medical conditions/diseases present before starting IMP are only considered AEs if they worsen after enrolment. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically relevant, or require therapy.

Once an AE is identified, the investigator should follow-up as specified below. Each time, the outcome should be documented and assigned to one of the following categories: not recovered/unchanged, condition deteriorating, recovered/resolved, improving/recovering, recovered/resolved with sequelae, fatal or unknown. The assessment of an AE should be made at each planned visit (or more frequently, if necessary). The investigator should document in the CRF any changes in seriousness, severity, the suspected relationship with the IMP, the interventions required to treat it, and the outcome.

Adverse events occurring between informed consent and the last visit

The investigator should follow up on all AEs which occurred from signature of study-specific informed consent until the last visit of the subject, at which point the outcome assessment is documented in the CRF.

Ongoing serious adverse events at the time of last visit

For any SAEs still ongoing at the time of last visit, the investigator should continue to follow-up until the SAE has resolved or has stabilized / is judged permanent for SAEs considered to be related to IMP (SADRs), and for up to 30 days after the last visit of subject for non-related SAEs. The investigator should send SAE follow-up reports to recipients as per the 'SAE Reporting' section 9.3.5 below.

Serious adverse events occurring after the last visit

Any SAEs experienced after the last visit should only be reported to sponsor if the investigator suspects a causal relationship to study treatment. The investigator must report the SADR to recipients as per the 'SAE Reporting' section 9.3.5 below.

9.3.5 SAE Reporting

It is **vitally important** that the investigator reports immediately, i.e., no later than 24 hours after awareness, any SAEs, or updates to previously reported SAEs, even if the investigator does not consider the AE to be drug-related.

The investigator should send SAE reports on the “Serious Adverse Event Report Form”, as initial or follow-up reports, *via* fax or email to the Country Patient Safety Head, and in copy to the project management (Lek Pharmaceuticals d.d.), to the addresses provided on the next page.

The investigator should also send all updates / new information on a new SAE Report Form as a follow-up to the previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if a diagnosis is available, if and how it was treated, and whether the subject continued or withdrew from study participation.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs.

Any new SAE (that is considered completely independent of a previously reported SAE) should be reported as a new and separate initial SAE report.

Any queries from the Country Patient Safety Head, Contract Research Organization (CRO) or sponsor/its representative regarding SAE reports should be answered by the investigator within 24 hours.

For more detailed information refer to the “Quick Reference Guide for Completing the SAE Form”.

The investigator should retain a delivery confirmation of the SAE reports for all recipients in the investigator study file.

10.2.3 Safety Endpoints

The safety endpoints in this trial are:

- Incidence and severity of adverse events
- Incidence and severity of drug-related adverse events
- Clinically relevant changes in laboratory parameters, vital signs, physical and ENT examination parameters from Visit 1 to Visit 6 (or early termination)
- Overall assessment of tolerability by patient and by investigator.

10.3 Populations for Analysis

Statistical analysis will be performed on three different patient populations:

- **Safety Set (SS),**
- **Full-Analysis Set (FAS),**
- **Per-Protocol Set (PPS)**.

10.3.1 Safety Set

The **Safety Set (SS)** is defined as all randomized patients who receive at least one dose of the trial medication. This will be the primary dataset for the evaluation of safety.

10.3.2 Full Analysis Set

The **Full Analysis Set (FAS)** is defined as all randomized patients who receive at least one dose of the trial medication and who have at least one post-baseline assessment of MSS during the double-blind treatment period. This will be the primary dataset for comparison of the primary endpoint.

If any subject terminates the trial before completing the 14 days of double-blind treatment the last available post-baseline assessment of the MSS will be carried forward until the virtual last observation point (**Last Observation Carried Forward or LOCF**).

The LOCF will also be used for calculating the secondary endpoints, if relevant.

10.3.3 Per Protocol Set

The **Per Protocol Set (PPS)** is defined as all FAS-evaluable patients who complete the double-blind treatment period without major protocol violations that could affect the efficacy evaluation. The latter will be prospectively defined before unblinding the trial.

Protocol violations will be documented in the Protocol Deviation Report. Individuals having any major violations will not be included in the per protocol set. All decisions regarding major deviations will be discussed and agreed between the statistician/medical team and the sponsor/its representative in the Blind Data Review Meeting, prior to unblinding and commencing the final analysis on the locked database.

10.4 Statistical Tests

[redacted] will write the **Statistical Analysis Plan (SAP)** for the present trial.

Efficacy:

Efficacy of the test product will be shown by testing superiority of the three different doses in a hierarchical test procedure from the highest to the lowest dose compared to placebo.

Hierarchical ordered hypotheses will be tested at the type I error rate of α=0.05 (two-sided) until the first non-rejection. No error rate adjustment is required.

The set of hypotheses is as follows:

H_{01}: $\mu_{2400} = \mu_{PL}$

H_{11}: $\mu_{2400} \neq \mu_{PL}$

H_{02}: $\mu_{1200} = \mu_{PL}$

H_{12}: $\mu_{1200} \neq \mu_{PL}$

H_{03}: $\mu_{600} = \mu_{PL}$

H_{13}: $\mu_{600} \neq \mu_{PL}$

Where μ notes “mean change from baseline in the daily MSS over the entire treatment period” for the respective strength.

Superiority of the Test treatment over placebo (PL) is confirmed if the p-value is < 0.05 and a positive treatment effect is shown.

For the primary efficacy an endpoint, analysis of covariance (ANCOVA) will be carried out using treatment and center as factors and baseline MSS as a covariate.

The trial will be powered to demonstrate superiority of the test product over placebo in the primary efficacy endpoint.

The confirmatory analysis of the primary endpoint will be performed in the FAS.

In addition, the analyses used for the primary efficacy endpoint will be performed in the PPS.

11 Trial Documentation

11.1 Source Documents

All originals or certified copies (dated and signed by the investigator) of measurements using medical devices, which routinely produce an image or print-out of the respective results (e.g. safety laboratory), will be considered as source documents.

All other data that cannot be derived from images/print-outs and are collected in the individual patient health medical record file in the clinical center will serve also as source data and will be transferred into the CRF as far as requested for the trial purposes.

Should the investigator enter any data first into any other kind of a document before transferring the data into the CRF, this other document becomes the source for the respective type of data.

A Trial Specific Source Form (TSSF) will be generated for the needs of the present trial and this document will be presented to the IEC/IRB and RA for approval. All TSSFs will be filed in the ITF and must be archived for at least 25 years after the trial has been completed.

According to Chapter 1.51 of ICH Topic E6 (R2)[3] - source data must be original records or certified copies of original records.

***"Certified copy** is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.[3]"*

As the 2nd page of CRFs and patient diaries is a duplex of the original (top) page of no-carbon copy paper signed and dated by the investigator, the 2nd page is considered as a certified copy.

In addition, the following data, which is obtained on the patient's informed consent form, is considered source data:

- date of birth of patient,
- screening number,
- participation in present clinical trial with identification of sponsor, trial number, and trial medication,
- date of signing informed consent.

The original patient's informed consent form (see also section 5.4) will be filed in the ITF and will remain at the investigational center for at least 25 years after the trial has been completed.

Additionally, the investigator must record the patient's trial participation in the subject medical health record/file.

NAME OF COMPANY: **HEXAL AG**	**NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP):** **Acetylcysteine 600 mg effervescent tablet**	**NAME OF ACTIVE INGREDIENT:** **acetylcysteine**
	smoking: ≥ 20 cigarettes daily) [24] Use of snuff tobacco [25] Legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the trial [26] Subjects who are known or suspected: – not to comply with the trial directives – not to be reliable or trustworthy – to be a dependent person, e.g. a relative, family member, or member/ employee of the investigator's or sponsor's staff – subject is in custody or submitted to an institution due to a judicial order.	
CLINICAL TRIAL CENTERS	Approximately 40 centers located in Germany, Bulgaria, Russia and Moldova.	
TEST PRODUCT	Name: Acetylcysteine 600 mg effervescent tablet Marketing authorization holder in Germany: HEXAL AG Marketing authorization No: [redacted] Formulation: effervescent tablet Active substance: acetylcysteine Strength: 600 mg acetylcysteine per effervescent tablet Dosing schedule: over 14 days **according to the randomized double-blind treatment** (*see randomization section*) Route of administration: oral; tablets should be taken during the meal (breakfast or lunch) dissolved in a glass of water (about 200 mL). Manufacturer: [redacted]	
PLACEBO TO TEST PRODUCT	Name: Placebo Formulation: effervescent tablet Active substance/ Strength: none Dosing schedule: over 14 days **according to the randomized double-blind treatment** (*see randomization section*) Route of administration: oral, tablets should be taken during the meal (breakfast or lunch) dissolved in a glass of water (about 200 mL). Manufacturer: [redacted]	

3 Table of Contents

In accordance with the national drug law all approvals needed for conducting the trial in the respective country will be obtained.

5.2 Regulatory Authorities

Prior to the initiation of the trial all relevant documents as required by the national legislation will be submitted to the regulatory authority(ies) (RA) responsible for the trial approval in the respective country.

In accordance with the national drug law all approvals needed for conducting the trial in the respective country will be obtained.

5.3 Protocol Modification

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information related to the scientific background of the trial.

All amendments must be discussed and signed by the sponsor/its representative, [redacted] and the coordinating investigator prior to implementation.

Amendments to the trial are regarded as "substantial"[5] where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the patients, or
- the scientific value of the trial.

In all cases, an amendment is only to be regarded as 'substantial' when one or both above criteria are met.

When the sponsor/its representative intends to make a substantial amendment to the protocol that would meet the above-mentioned criteria, he should notify [redacted]. The sponsor/its representative authorizes [redacted] to supervise all necessary notifications to the ECs and RAs and to receive all approvals needed before an amendment is implemented.

Amendments which might have an impact on the safety, physical or mental integrity of the patients (and/or could influence on the patients' decision to participate in the trial) require new patient information and a new informed consent/ assent form that is to be signed by all patients enrolled in the trial who are affected by the amendment.

In case of minor changes to the protocol (administrative, logistical), the non-substantial amendment will be prepared and signed by both [redacted] and sponsor or its representative. A written approval of sponsor/its representative before implementation is required, however not from ECs and RAs.

The number of patients under high-dose NAC was over 1400, the oral dose regimen ranged from 1200 mg/d up to 6000 mg/d, and the duration of studies from 16 days to 60 months. Most of the studies used the dose around 2000–2400 mg per day, which appeared to be effective and well tolerated, with no significant between-group differences observed in most of the controlled trials. Gastrointestinal symptoms were the most common adverse events, including mild abdominal pain, mild abdominal discomfort, heartburn, flatulence, cramps, nausea, vomiting, and diarrhea.

These results have been confirmed in a recent review by Ooi et al. (2018)[32] concluding that oral NAC is safe and well tolerated without any considerable adverse effects. Current evidence supports its use as an adjunctive therapy for psychiatric conditions, administered concomitantly with existing medications, with a recommended dosage between 2000 and 2400 mg per day.

- **Cardioprotection**

A meta-analysis investigating whether NAC can prevent postoperative atrial fibrillation (POAF) after cardiac surgery examined 10 randomized controlled trials enrolling a total of 1026 patients. The dose regimen included, among others, 1200 mg b.i.d. p.o. In one of the trials the total dose of NAC administered intravenously over a period of 24 hours was 300 mg/kg, corresponding to 21000 mg for a person with 70 kg body weight. In this meta-analysis, NAC had a generally good safety profile, with no statistical difference being found when compared with control groups (Liu et al., 2014)[33].

- **Systemic lupus erythematosus**

In a randomized, double-blind, placebo-controlled study, a total of 36 patients with systemic lupus erythematosus received either daily placebo or 1200, 2400 or 4800 mg of NAC p.o. for 3 months. NAC dosages up to 2400 mg daily were well tolerated by all patients (Lai et al. 2012)[34].

Summarizing this body of evidence, it can be stated that the intake of 1200 mg acetylcysteine given as 2 tablets of 600 mg twice daily (for a total of 2400 mg daily) over a short period of 14 days appears to pose no safety risk.

This conclusion holds true for adults as well as for adolescents, based on recently published studies. A randomized controlled trial of pharmacotherapy for cannabis dependence in 116 adolescents revealed that the NAC dose of 1200 mg twice daily over 8 weeks was well tolerated, with minimal adverse events (Gray et al. 2012)[35]. Similarly, Ghanizadeh et al. (2017)[36] demonstrated NAC to be an effective add-on to citalopram in improving resistance/ control to compulsions in children and adolescents with obsessive-compulsive disorder in a double-blind, placebo-controlled trial with 34 pediatric patients. Significant reduction in the score of resistance/control to obsessions was detected in the intervention group after supplementing with NAC (titrated up to 2400 mg/day) for 10 weeks. NAC was well tolerated and the rates of adverse effects were not different between NAC and placebo groups.

screening visit

[12] Intranasal or systemic use of antibiotics within 30 days prior to screening visit

[13] Use of nasal decongestants within 2 days prior to screening visit

[14] Concomitant treatment of common cold-like symptoms within 7 days prior to screening visit with any of the following:

a) Analgesics
b) Non-steroidal anti-inflammatory drugs
c) Antihistamines

[15] Concomitant use of intranasal saline irrigation

[16] Use of immunosuppressive agents within 30 days prior to screening visit

[17] Immunocompromised state

[18] Suspicion for acute bacterial rhinosinusitis (defined as presence of purulence for 3 to 4 days with fever ≥ 38.3°C)

[19] Pregnant or breast-feeding female patient

[20] Female patient of childbearing potential (not surgically sterilized/ hysterectomized or postmenopausal for at least 1 year) who is not currently using (documented at screening visit) and not willing to use medically reliable methods of contraception for the entire trial duration such as oral, injectable or implantable contraceptives, intrauterine contraceptive devices (IUD), sexual abstinence or vasectomized partner

[21] Any other condition of the patient (e.g. serious or unstable medical or psychological condition, acute psychosis) that in the opinion of the investigator may compromise evaluation of the trial treatment or may jeopardize patient's safety, compliance or adherence to protocol requirements

[22] Participation in ANY research study involving another investigational medicinal product (IMP) within 30 days prior to screening visit, or simultaneous participation in another clinical study or previous participation in present study

[23] Suspected alcohol/ drug dependence or abuse (including heavy smoking: ≥ 20 cigarettes daily)

[24] Use of snuff tobacco

[25] Legal incapacity and/or other circumstances rendering the patient unable to understand the nature, scope and possible consequences of the trial

[26] Subjects who are known or suspected:

- not to comply with the trial directives
- not to be reliable or trustworthy
- to be a dependent person, e.g. a relative, family member, or member/ employee of the investigator's or sponsor's staff
- subject is in custody or submitted to an institution due to a judicial order.

9 Trial Procedures

The visit schedule and planned assessments for each visit in tabulated form are presented in section 2.1 and 2.2.

The trial duration will last about 16 days for a single patient. A total number of 6 ambulatory visits is planned for the present trial (see description below).

VISIT 1 will be carried out 1 day before the start of treatment (Day 1) and includes the documentation of the following **screening examinations**:

- date of signing the informed consent
- date and time of examination (visit)
- patient identification by means of national ID card or another national ID document
- demographic data: birth date, ethnicity, gender, height, weight
- life style and habits: consumption of alcohol, nicotine, history of drug abuse or use of illegal drugs
- history of primary disease (acute, uncomplicated rhinosinusitis)
- **Major Symptom Score (MSS) assessment by the patient (transcribed by the investigator from the Trial Specific Source Form (TSSF) into the CRF)**
- medical and surgical history (anamnesis) for documentation of the following:
  - concomitant diseases and concomitant therapies/ medication(s) documented at Visit 1;
  - previous diseases and surgeries and previous therapies/ medication(s) within the last 6 months prior to screening Visit 1;
  - medical or other therapeutical measures/ actions used currently by the patient (e.g. sinus lavage, intranasal saline irrigation)
  - additional anamnestic information concerning:
    last participation in any clinical trial,
    last administration of any investigational drug,
    allergy (e.g. perennial or seasonal rhinitis),
    drug hypersensitivity or intolerance,
    hypersensitivity or intolerance to acetylcysteine or any of the excipients of the trial medication,
    check for hereditary fructose intolerance, galactose intolerance, lactase deficiency or glucose-galactose malabsorption.
- for female patient of childbearing potential: information on use of any contraception, method of contraception used [e.g. oral, injectable or implantable contraceptives, intrauterine contraceptive devices (IUD), pre-existing sterilization with date of sterilization, or sexual abstinence or vasectomized partner] and for postmenopausal female patient the date of last menstrual bleeding will be documented.
  Where a contraceptive medication is used, a specification of the drug name, dosage/route, start, ongoing and end of treatment is to be documented.
- vital signs measurements of body temperature with documentation of the measuring method used, pulse rate, and blood pressure after 5 minutes rest in sitting position

TT 1 Addresses for SAE reporting

Country Patient Safety Head, for Bulgaria: email: [redacted] fax: [redacted]
Country Patient Safety Head, for Germany: email: [redacted] fax: [redacted]
Country Patient Safety Head, for Moldova: email: [redacted] fax: [redacted]
Country Patient Safety Head, for Russia: email: [redacted] fax: [redacted]
[redacted] (Lek Pharmaceuticals d.d.): [redacted] PhD email: [redacted] [redacted] Dipl. Biol. email: [redacted]

The responsible contact persons for questions are:

[redacted] (Lek Pharmaceuticals d.d.) [redacted] Phone [redacted]	[redacted] (Lek Pharmaceuticals d.d.) [redacted] PhD Phone: [redacted] [redacted], MD, PhD Phone: [redacted]

Investigator Notification and 6 monthly line listings

If a SADR is not listed in the Reference Safety Information (SmPC), the sponsor may urgently require further information from the investigator for Health Authority reporting.

The sponsor may, if applicable, issue Investigator Notifications and 6 monthly line listings of Suspected Unexpected Serious Adverse Reactions (SUSARs) to all investigators concerned with any study with the same IMP.

The submission of these Investigator Notifications and 6-monthly line listings, if applicable, to local IRBs / Ethics Committees is the responsibility of the investigator (supported by the CRO) as stipulated in the study contract. The submission of Investigator Notifications and 6-monthly line listings to national Ethics Committee is the responsibility of the CRO, if applicable.

Health authority reporting

The sponsor/its representative will submit all reportable cases within the requested timelines to all concerned health authorities.

This analysis is intended to provide supportive evidence and will be considered descriptive.

Safety:

The Safety Set will be used for the analysis of the safety data. All safety data obtained in this trial will be tabulated descriptively with descriptive group statistics (mean, standard deviation, minimum, maximum, number of valid cases) where appropriate.

AEs will be summarized by primary system organ class (SOC) and preferred term (PT). Severity and drug-event relationship of treatment emergent AEs are summarized separately. All adverse events will be listed.

Vitals signs, including changes from baseline will be summarized. A frequency table will be presented for abnormal values of laboratory parameters.

10.5 Calculation of Sample Size

The sample size is calculated in respect of the primary endpoint. For the calculation of sample size following parameters were taken into consideration based on data published by Jund et al. (2015)[1]:

α	= 0.05 (two-sided)
ß	= 0.20 (power = 80%)
mean MSS change (test)	= 5.4
mean MSS change (placebo)	= 4.5
Standard deviation	= 3.4
Randomization ratio	= 1 (1:1:1:1, 3 doses of test *vs.* placebo)
Sample size per group:	= 225 subjects

The numbers above refer to the FAS.

The resulting number of patients to be randomized in each of the groups is approximately 225. The total number of patients to be randomized is thus equal to 900.

10.6 Coding and Randomization

The randomization code will be generated by a company subcontracted by the sponsor and otherwise not involved in the present trial ([redacted], using the program [redacted]

The randomization code will be kept confidential at the sponsor, in a sealed envelope with no access for personnel involved in the study conduct.

The Blind Data Review Meeting (BDRM) will be held after closure of the database and before unblinding the trial. The decisions taken at this meeting will be documented in a respective protocol. Only after the BDRM protocol is signed by the parties involved and all database activities are completed, the unblinding will be possible. The sponsor/its representative will be asked to give an approval for the study unblinding. The randomization code will be included in the Trial Master File (TMF) along with correspondence concerning the study unblinding.

11.2 Case Report Form (CRF)

A paper-based CRF will be used in this trial. [redacted] will design the CRF in close co-operation with the sponsor. The CRFs will be written in English.

The CRFs will be printed on a double no-carbon copy paper (for details, please refer to section 9.5.3).

The investigator will ensure that all data are entered promptly, completely, and accurately and conform to the source documents. This also applies to the data for screening failures, i.e. patients who have not fulfilled the eligibility criteria and thus are not enrolled into the trial.

Even if there are no changes from a previous examination, the questions which are repeated in each CRF chapter should be fully answered for all patients continuing their study participation.

11.3 Patient Diary

A paper-based patient diary containing the MSS and SNOT-22 questionnaire will be used in this trial. [redacted] will design the diary in close co-operation with the sponsor.

The diary template will be written in English and will then be translated into the local languages of the countries involved in the trial. The patients will always use the local version of the diary.

The patient diary will be printed on a double no-carbon copy paper (for details, please refer to section 9.5.3).

11.4 Investigator's File

[redacted] will provide each principal investigator with an investigator trial file specific to the trial and clinical center.

As required according to ICH Topic E 6[3], all essential documents for the conduct of the clinical trial will be filed therein. These documents will serve to demonstrate the compliance of the clinical center personnel with the standards of GCP and all applicable regulatory requirements. The investigator trial file will be archived in the clinical center.

11.5 Trial Master File

[redacted] will maintain and archive all essential documents for the conduct of the clinical trial in a trial master file as required according to ICH[3].

These documents will serve to demonstrate the compliance of all parties involved in the clinical trial with the standards of GCP and all applicable regulatory requirements.