Official Title: Efficacy and Safety of Acetylcysteine for the Treatment of Acute Uncomplicated Rhinosinusitis: a Prospective, Randomized, Double-blind, Placebo-controlled Trial

NCT Number: NCT04123405

Document Date: Clinical Study Protocol Version 5: 14 August 2020

CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 5.0

TITLE

Efficacy and safety of acetylcysteine for the treatment of acute uncomplicated rhinosinusitis: a prospective, randomized, double-blind, placebo-controlled trial

Release date of protocol:	**24-Apr-2019**	
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Development phase:	**III**	

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Trial No.:
HEXAL AG 2018-08-EFT-1
[redacted] C1018001

EudraCT No.:
2019-000060-20

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*In Case of any Serious Adverse Event or Emergency, please refer to the contact data in section **9.3.5**.*

1 Signatures of Coordinating Investigator and Other Parties Involved

1.1 Coordinating Investigator

I, herewith, confirm that the trial protocol contains all the information and rules necessary to conduct the study according to Good Clinical Practice (GCP) and that the trial “Efficacy and safety of acetylcysteine for the treatment of acute uncomplicated rhinosinusitis: a prospective, randomized, double-blind, placebo-controlled trial” will be carried out and documented in complete compliance with, the national laws and regulations and the Declaration of Helsinki and the GCP guideline.

I recognize that all information concerning this trial is not previously published and is a confidential information. This includes the SmPC, trial protocol, case report forms, assay methods, technical methodology, and scientific data.

The investigators will be informed about the pharmacological/toxicological tests and all new knowledge about the IMP as well as about any newly occurring, hitherto unknown adverse reactions of the test IMPs as soon as the information is available.

I recognize that any changes in the protocol must be approved in writing by the coordinating investigator, principal investigator(s), HEXAL AG or its representative Lek Pharmaceuticals d.d., the Ethics Committee (IEC/IRB) and national regulatory authority before implementation except when necessary to eliminate immediate hazards to the subjects.

By my signature below, I hereby certify that I have more than 2 years of experience in the conduct of clinical studies and that I have read, understood and agree to abide by all conditions, instructions, and restrictions contained in the protocol number 2018-08-EFT-1/C1018001 dated 14-Aug-2020 and also that I was trained in the sponsor’s serious adverse event (SAE) and pregnancy reporting obligations.

Name: [redacted]

Address: [redacted]

Phone: [redacted]
Fax: [redacted]
Email: [redacted]

Signature of Coordinating Investigator, Date

1.2 Principal Investigator

I, herewith, confirm that the trial “Efficacy and safety of acetylcysteine for the treatment of acute uncomplicated rhinosinusitis: a prospective, randomized, double-blind, placebo-controlled trial” will be carried out and documented in the CRFs in complete compliance with the national laws and regulations and the Declaration of Helsinki and the Good Clinical Practice (GCP) guideline.

I recognize that all information concerning this trial is not previously published and is a confidential information. This includes the SmPC, trial protocol, case report forms, assay methods, technical methodology, and scientific data.

I recognize that any changes in the protocol must be approved in writing by the coordinating investigator, principal investigator(s), HEXAL AG or its representative Lek Pharmaceuticals d.d., Ethics Committee (IEC/IRB) and national regulatory authority before implementation except when necessary to eliminate immediate hazards to the subjects.

By my signature below, I hereby certify that I have more than 2 years of experience in the conduct of clinical studies and that I have read, understood and agree to abide by all conditions, instructions, and restrictions contained in the protocol number 2018-08-EFT-1/C1018001 dated 14-Aug-2020 and also that I was trained in the sponsor’s serious adverse event (SAE) and pregnancy reporting obligations.

Name: …….

Name of Clinical Center: …….

……..

Address of Clinical Center: …….

……..

……..

……..

Phone: …….

Fax: …….

Email: …….

_____

Signature of Principal Investigator, Date

1.3 Sub-Investigator

I, herewith, confirm that the trial “Efficacy and safety of acetylcysteine for the treatment of acute uncomplicated rhinosinusitis: a prospective, randomized, double-blind, placebo-controlled trial” will be carried out and documented in complete compliance with, the national laws and regulations and the Declaration of Helsinki and the Good Clinical Practice (GCP) guideline.

I recognize that all information concerning this trial is not previously published and is a confidential information. This includes the SmPC, trial protocol, case report forms, assay methods, technical methodology, and scientific data.

I recognize that any changes in the protocol must be approved in writing by the coordinating investigator, principal investigator(s), HEXAL AG or its representative Lek Pharmaceuticals d.d., Ethics Committee (IEC/IRB) and national regulatory authority before implementation except when necessary to eliminate immediate hazards to the subjects.

By my signature below, I hereby certify that I have more than 2 years of experience in the conduct of clinical studies and that I have read, understood and agree to abide by all conditions, instructions, and restrictions contained in the protocol number 2018-08-EFT-1/C1018001 dated 14-Aug-2020 and also that I was trained in the sponsor’s serious adverse event (SAE) and pregnancy reporting obligations.

Name: …….

Name of Clinical Center: …….

……..

Address of Clinical Center: …….

……..

……..

……..

……..

_____

Signature of Investigator, Date

1.4 Contract Research Organization (CRO)

[redacted]
[redacted] MD, PhD
[redacted]

_____

Signature, Date

[redacted]**AUTHOR OF TRIAL PROTOCOL:**
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[redacted]

_____

Signature, Date

[redacted] **(Medical Expert):**
[redacted] MD, PhD
[redacted]

_____

Signature, Date

[redacted]
[redacted] M.Sc. Biotech.
[redacted]

_____

Signature, Date

[redacted]

[redacted], Dipl. Math. (FH)
[redacted]

_____

Signature, Date

[redacted]

[redacted] Dipl. Biol., PhD
[redacted]

_____

Signature, Date

1.5 Project Management and Sponsor Representative

[redacted]

Lek Pharmaceuticals d.d.

[redacted]

_____

Signature, Date

[redacted]

Lek Pharmaceuticals d.d.

[redacted], PhD

_____

Signature, Date

1.6 Trial Administrative Structure

Sponsor:	HEXAL AG Industriestraße 25 83607 Holzkirchen Germany Phone: Fax:
Project Management and Sponsor Representative,	Lek Pharmaceuticals d.d. Verovškova 57 1526 Ljubljana Slovenia Phone Mobile:
Project Management and Sponsor Representative,	PhD Lek Pharmaceuticals d.d. Verovškova 57 1526 Ljubljana Slovenia Phone: Email:
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Local CRO in BULGARIA (*on behalf of* [redacted] *responsible for monitoring and submission to / correspondence with Ethics Committee and Regulatory Authority)*	[redacted] Phone: [redacted] Fax: [redacted] Email: [redacted]
Local CRO in MOLDOVA (*on behalf of* [redacted] *responsible for monitoring and submission to / correspondence with Ethics Committee and Regulatory Authority)*	[redacted] Mobile: [redacted] Mobile: [redacted] Email: [redacted]
Local CRO in RUSSIA (*on behalf of* [redacted] *responsible for monitoring and submission to / correspondence with Ethics Committee and Regulatory Authority)*	[redacted] Phone: [redacted] Email: [redacted]

2 Trial Synopsis and Schedule of Assessments

2.1 Trial Synopsis

NAME OF COMPANY: **HEXAL AG**	**NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP):** **Acetylcysteine 600 mg effervescent tablet**	**NAME OF ACTIVE INGREDIENT:** **acetylcysteine**
TITLE OF TRIAL	Efficacy and safety of acetylcysteine for the treatment of acute uncomplicated rhinosinusitis: a prospective, randomized, double-blind, placebo-controlled trial	
TRIAL NUMBER	2018-08-EFT-1 (sponsor) / C1018001 (CRO)	
PHASE	Phase III	
INDICATION	Acute uncomplicated rhinosinusitis	
TRIAL DESIGN	Prospective, randomized, multinational, multicenter, double-blind study in 4 parallel groups of patients	
PRIMARY OBJECTIVE	To assess the efficacy of three different total daily doses of the investigational medicinal product containing 600 mg acetylcysteine per effervescent tablet compared to placebo for the treatment of acute uncomplicated rhinosinusitis.	
SECONDARY OBJECTIVES	To assess the safety and tolerability of three different total daily doses of the investigational medicinal product containing 600 mg acetylcysteine per effervescent tablet compared to placebo for the treatment of acute uncomplicated rhinosinusitis.	
CONTRACT RESEARCH ORGANIZATION	[redacted] Phone: Fax:	
PLANNED SAMPLE SIZE	Approximately 900 patients will be randomized in 4 different groups of approximately 225 subjects each: three different total daily doses of the test product, or placebo.	
SUBJECTS SELECTION CRITERIA	**Inclusion criteria:** [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;	

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	

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]	

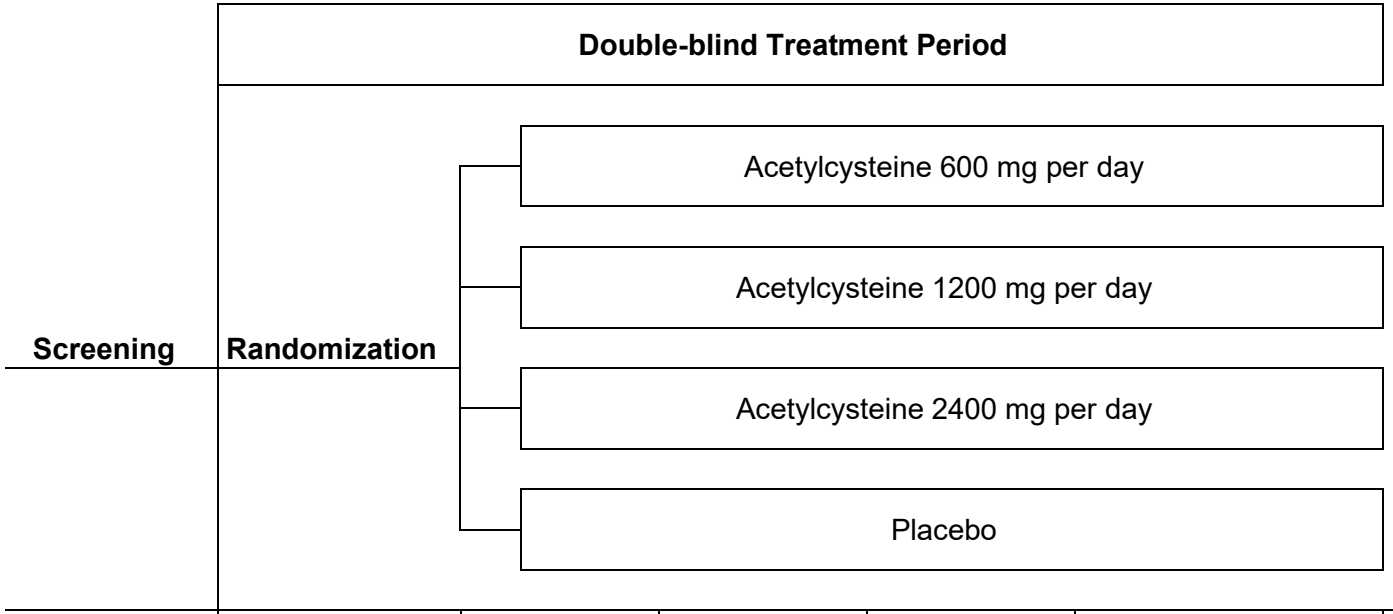
NAME OF COMPANY: **HEXAL AG**	**NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP):** **Acetylcysteine 600 mg effervescent tablet**	**NAME OF ACTIVE INGREDIENT:** **acetylcysteine**
BLINDING	**The present trial will be double-blind**. The tablets containing the Test product and Placebo will be identical in their appearance and the labels will not contain any information about the identity of the respective product. To maintain blinding, all patients will receive 4 tablets per day (2 tablets in the morning and 2 tablets at noon) provided in a daily kit.	
RANDOMIZATION	Patients will be allocated to identification numbers in sequential order according to their admission to the trial. Patients who meet the inclusion/ no exclusion criteria will be randomized to double-blind treatment with one of the following: ➢ Group A: 600 mg acetylcysteine: one tablet test product plus three tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR* ➢ Group B: 1200 mg acetylcysteine: two tablets test product plus two tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR* ➢ Group C: 2400 mg acetylcysteine: four tablets test product per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR* ➢ Group D: Placebo: four tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily).	
DURATION OF TREATMENT	Patients will undergo screening examinations at Visit 1. Patients who meet all inclusion/ no exclusion criteria will be randomized at the baseline visit (Visit 2) to the double-blind treatment for a duration of 14 days but in case of delayed final visit (Visit 6) the patient can voluntarily take reserve study medication for a maximum of 3 additional days. After the end of the double-blind treatment phase, the patients will undergo an end-of-treatment (EOT) examination at Visit 6 on Day 15 (+3). A follow-up phone call within 7 days after Visit 6 (or earlier in case of premature termination) will be performed for all patients.	
CONCOMITANT MEDICATION/ OTHER THERAPEUTIC MEASURES	**<u>Not allowed</u>:** • Intranasal or systemic use of corticosteroids within 30 days prior to screening visit and during the trial; • Intranasal or systemic use of antibiotics within 30 days prior to screening visit and during the trial; • 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.	

NAME OF COMPANY: HEXAL AG	NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP): Acetylcysteine 600 mg effervescent tablet	NAME OF ACTIVE INGREDIENT: acetylcysteine
	• Therapeutic measures available at home, e.g. 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. **Allowed:** • Other long-term therapy for any chronic disease (if expected to remain stable for the duration of the entire trial).	
EFFICACY PARAMETERS	**Patient's assessments:** • **Major Symptom Score (MSS):** MSS will be assessed by the patient at screening (**Visit 1**) and immediately before randomization (**Visit 2; this will constitute the baseline value**). Both MSS assessments will be transcribed from the Trial Specific Source Form (TSSF) into the CRF. Thereafter, the patient will document the 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). The last MSS will be will be assessed by the patient during Visit 6 and transcribed into the CRF**.** • **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. **Investigator's assessments:** • **Investigator's assessment of the overall response to treatment:** The investigator will assess the overall response to treatment at each visit after baseline: on Day 4 (Visit 3), Day 7 (Visit 4), Day 10 (Visit 5), and Day 15 (Visit 6).	
SAFETY PARAMETERS	• **Adverse events (AEs):** AEs 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). AEs will be assessed for seriousness, severity and drug-event relationship. • **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 Day 4 (Visit 3), Day 7 (Visit 4), Day 10 (Visit 5), and Day 15 (Visit 6). • **Safety laboratory:** Hematology and blood chemistry at screening (Visit 1) and at Visit 6. In all female patients a serum pregnancy test for measurement of human chorionic gonadotropin (hCG) will be performed at screening (Visit 1) and at Visit 6. • **Overall assessment of tolerability by the patient and by the investigator** on Day 7 (Visit 4) and Day 15 (Visit 6).	
PRIMARY ENDPOINT	Mean change from baseline in the daily MSS over the entire treatment period: $$\frac{1}{14}\sum_{i=Day\ 2}^{Day\ 15}\left(x_i - x_{Day\ 1\ (baseline)}\right)$$	

NAME OF COMPANY: **HEXAL AG**	**NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP):** **Acetylcysteine 600 mg effervescent tablet**	**NAME OF ACTIVE INGREDIENT:** **acetylcysteine**
SECONDARY ENDPOINTS	• Time to onset of action defined as first day of active treatment on which MSS shows statistically significant difference from placebo • MSS development over the course of the study • SNOT-22 by visit and changes versus baseline • Percentage of responders and non-responders to treatment based on the assessment of overall response to treatment by the investigator.	
SAFETY ENDPOINTS	• 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.	
DATASETS FOR STATISTICAL ANALYSIS	• **Safety Set:** all randomized patients who received at least one dose of the trial medication. • **Full-Analysis Set (FAS):** all randomized patients who received 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. • **Per-Protocol Set (PPS):** all FAS-evaluable patients who completed the double-blind treatment period without major protocol violations that could affect the efficacy evaluation.	
STATISTICAL ANALYSIS	**Efficacy:** Efficacy of the test product will be shown by testing superiority of the three different doses in a hierarchical test procedure starting 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. 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. This analysis is intended to provide supportive evidence and will be considered descriptive.	

NAME OF COMPANY: HEXAL AG	NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP): Acetylcysteine 600 mg effervescent tablet	NAME OF ACTIVE INGREDIENT: acetylcysteine
	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. This will include also the overall assessment of tolerability by the patient and by the investigator on Day 7 (Visit 4) and Day 15 (Visit 6). 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. Vital signs, including changes from baseline will be summarized. A frequency table will be presented for abnormal values of laboratory parameters.	
CALCULATION OF SAMPLE SIZE	The sample size is calculated in respect of the primary endpoint. For the calculation of sample size, the 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 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.	

2.1 Flow Chart



Day -1[*]	*Day 1*	*Day 4*	*Day 7*	*Day 10*	*Day 14*	*Day 15 (+3)*	*Follow-up Phone Call*
VISIT 1	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**	**no visit**	**VISIT 6**	
SCREENING	**START OF TREATMENT** *In the morning between 7 and 9 a.m.*				**LAST DAY OF TREATMENT** *[but in case of delayed Visit 6 the patient can voluntarily take reserve study medication for a maximum of 3 additional days]*		*within 7 days after Visit 6 (or earlier in case of premature termination)*

[*] presence of symptoms ≤3 days prior to Visit 1 (screening)

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		●	●	●	●	●	●

3 Table of Contents

3.1 Figures Referred to in the Text

4 List of Abbreviations and Definitions of Terms

ADR	Adverse drug reaction
AE	Adverse event
ARS	Acute rhinosinusitis
ATC	Anatomical therapeutic chemical classification system
b.i.d	Twice a day
BDRM	Blind Data Review Meeting
CDMS	Clinical data management system
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products
CR	Clinically relevant
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
DMP	Data management plan
ENT	Ears, Nose, Throat
EOT	End of treatment
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC/ IRB	Independent Ethics Committee/ Institutional Review Board
IMP	Investigational medicinal product
ITF	Investigator's trial file
MCH	Mean corpuscular Haemoglobin
MCHC	Mean cell Haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	Millimeter
mmHg	Millimeters of mercury
MSS	Major Symptom Score
NA	Not applicable
NAC	N-acetylcysteine
NCR	Not clinically relevant
p.	Page
p.o.	Oral
PPS	Per protocol set
PT	Preferred term
QMD	Quality management department
RA	Regulatory authority
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SmPC/SPC	Summary of product characteristics
SNOT	Sino-Nasal Outcome Test (questionnaire)
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TSSF	Trial Specific Source Form
V	Visit
WHO	World Health Organization
WMA	World Medical Association

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.

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.

5.4 Patient Information and Informed Consent

Before being enrolled into the trial, patients must have consented to participate in response to a complete written and verbal explanation of the nature, scope and possible consequences of the trial by a physician in a form and language understandable to them.

The patients must be able to understand the full implications of their decision.

The patient information and informed consent will be prepared by [redacted] and will be translated into the respective local language of the clinical center(s) whereby the translated documents will be used for confirmation of the patient's consent by the signature of the investigator, the patient and in case of adolescents by the signatures of the parent(s)/ guardian(s).

For adult patients (≥18 years) the informed consent to participate in the trial must be provided in written form.

For adolescent patients (≥14 - <18 years) the own subject informed consent/ assent to participate in the trial must be provided in written form with the mandatory written informed consent from all parent(s)/ legal guardian(s).

The patient information and informed consent will explain the nature of the trial, its objectives and potential risks. Both the informed consent discussion and the written informed consent form and any other written information to be provided to patients will include explanations of the points mentioned in section 4.8.10 of the ICH Guidance on Good Clinical Practice E6(R2) (CPMP/ICH/135/95)[3].

Personal information will be treated as strictly confidential and will not be publicly available.

As required by the ICH-GCP guideline, the patient authorizes in written form that the patient’s original medical records may be verified by the CRA(s), the auditor(s), and the regulatory authorities by direct access in accordance with the applicable laws and regulations.

As required by the ICH-GCP guideline, the trial specific information for patients and informed consent will be received as one original and enough ample time will be given to the patients to read the document. The personally signed and dated original will remain with the investigator as part of the confidential data and will be kept there (in the ITF) for at least 25 years after the trial has been completed. A certified copy of the personally signed and dated original will be handed over to the patient.

To ensure medical confidentiality and data protection, the patient identification and all other essential documents as addressed in chapter 8 of the ICH-GCP guideline will be located in the ITF and must be archived for at least 25 years after the trial has been completed (please refer to protocol sections 9.5.3, 11.1 and 11.7).

The individual medical health records/ files of the clinical center(s) shall be kept for the maximum period of time permitted by the national law of the country of the clinical center. Image carriers or other data carriers can be used for storage.

The investigator will allow these documents to be inspected on request and will affirm - by signing and dating - in the case report forms that informed consent has been obtained before start of any trial-related procedure(s).

The investigator will not undertake any investigations specifically required only for the trial until valid consent has been obtained.

5.5 Patient Insurance

Every subject is insured in accordance with the provisions of the national law of the countries involved against damage to health which might occur during the conduct of the clinical trial and the material damages which might occur in connection thereto.

Excluded from the insurance cover are damages to health and worsening of previous existing diseases which would have occurred or continued if the patient had not taken part in the clinical trial. Following the clauses of the insurance, the insured patients are to be informed about the existence of the insurance contract.

A copy of the insurance certificate will be filed in the investigator's trial file (ITF).

5.6 Patient's Confidentiality

To maintain patient's confidentiality, all data recorded during the trial will be identified by patient's screening/ randomization number and patient's date of birth. However, the investigator agrees to record the complete patient identification. This information will be treated with strict adherence to confidentiality and will be filed in the investigator's trial file (ITF).

6 Introduction

6.1 Acute Rhinosinusitis

Acute rhinosinusitis (ARS) is a very common condition that is primarily managed in primary care. Prevalence rates vary from 6-15% depending on the study parameters, although studies specifying ARS report 6-12%, with a prevalence of recurrent ARS estimated at 0.035%.

The primary causes of ARS are viruses with 0.5-2.0% of patients developing acute bacterial rhinosinusitis secondary to a viral infection. Prevalence of ARS varies with season (higher in the winter months) and climatic variations, and increasing with a damp environment and air pollution (European Position Paper on Rhinosinusitis and Nasal Polyps; Fokkens et al., 2012[12]).

ARS in adults is defined as:

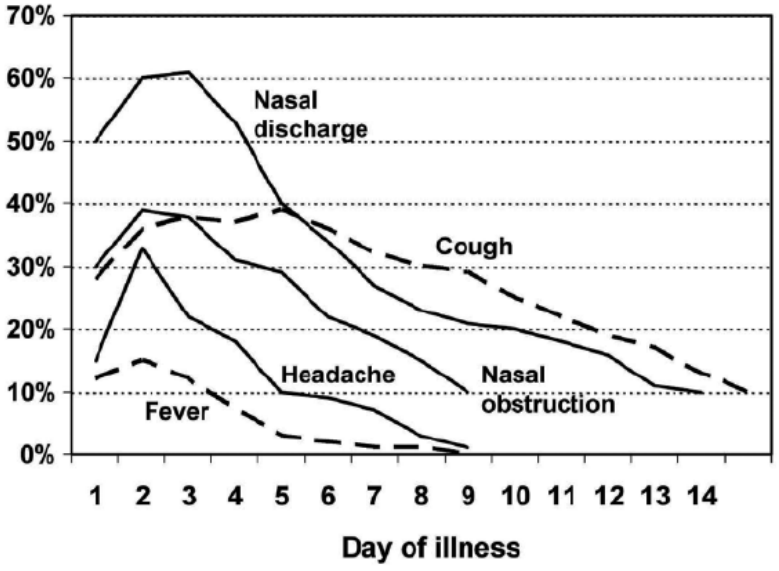
Sudden onset of two or more symptoms:

- nasal blockage/ obstruction/ congestion
- or nasal discharge (anterior/posterior nasal drip)
- ± facial pain/pressure
- ± reduction or loss of smell

for <12 weeks.

ARS can be sub-divided into “acute viral rhinosinusitis (synonymous with “common cold”), in which the duration of symptoms is less than 10 days, usually a self-limiting condition that frequently does not present to clinicians, and “acute post-viral rhinosinusitis”, defined by an increase in symptoms after 5 days or persistence beyond 10 days.

Typical symptoms of spontaneous rhinovirus infections peak at days 2 to 3 and wane thereafter but may persist 14 days or longer. Symptoms of viral rhinosinusitis may persist for longer than 10 days, but they gradually decrease in severity (see figure below taken from Rosenfeld et al., 2015[13]; US Clinical Practice Guideline on Adult Sinusitis).



According to the German Society of General Practice/Family Medicine (DEGAM, 2017[14]), viral rhinosinusitis episodes are clinically cured after a maximum of three weeks.

A clinician should diagnose acute “bacterial” rhinosinusitis (ABRS) when symptoms or signs of acute rhinosinusitis persist without evidence of improvement for at least 10 days beyond the onset of upper respiratory symptoms.

Fever is present in some patients with viral rhinosinusitis in the first few days of illness but does not predict bacterial infection as an isolated diagnostic criterion. Fever has a sensitivity and specificity of only about 50% for ABRS.

Adjunctive treatments for rhinosinusitis that may aid in symptomatic relief include analgesics, decongestants (α-adrenergic), corticosteroids, saline irrigation, and mucolytics. None of these products has been specifically approved by the FDA for use in ARS (as of March 2014), and only some have data from controlled clinical studies supporting this use. Moreover, existing trials often include co-interventions and a heterogeneous population of patients with viral, recurrent bacterial, chronic, and allergic rhinosinusitis.

With regard to mucolytics the “European Position Paper on Rhinosinusitis and Nasal Polyps[12]” states:

“*Mucolytics are used as adjuncts to antibiotic and/or decongestant treatment in ARS in order to reduce the viscosity of sinus secretion. Although some drugs have been shown to have mucolytic effect and were recommended as adjunct treatment for ARS, the benefit of such treatment is not clear due to the lack of standardization in pharmacodynamic and pharmacokinetic properties of these drugs, and also double-blinded, placebo-controlled (DBPC) randomized studies to prove their efficacy. In future, more standardization of mucolytics and larger scale DBPC randomized studies still need to be done in order to fully assess the efficacy of mucolytics in the treatment of ARS*.”

This position is also transparent in the current guideline on rhinosinusitis of the “German Society of General Practice/Family Medicine” (DEGAM, 2017), stating that mucolytics like acetylcysteine or ambroxol are commonly used as adjunctive therapies, although the benefit of these medications lacks clinical evidence.

6.2 Mode of Action of Acetylcysteine

Acetylcysteine (NAC) is the N-acetyl derivative of the amino acid L-cysteine and a precursor in the formation of the antioxidant glutathione in the body. The thiol (sulfhydryl) group confers antioxidant effects and is able to reduce free radicals. The mucolytic activity of NAC is considered to be dual in origin:

(1) its sulfhydryl group breaks the disulfide bonds between the mucopolysaccharide fibers, and

(2) disrupts polymerization bonds of DNA fibers (in purulent mucus).

These mechanisms are thought to decrease the viscosity of the mucus.

Oral preparations containing up to 600 mg of NAC as a single dose have been marketed by pharmaceutical companies within the EU to a large extent for many decades, with recognized efficacy and proven safety in the mucolytic treatment of lower respiratory pathologies such as acute and chronic bronchitis and related diseases.

6.3 Clinical Use of Acetylcysteine for Indication Sinusitis

Pharmacotherapeutic group: Cough and cold preparations; Mucolytics (SmPC ACETYLCYSTEINE 600 MG EFFERVESCENT TABLET[15])

ATC code: R05CB01

Therapeutic indications: Secretolytic therapy in acute and chronic bronchopulmonary diseases accompanied by impaired formation and transport of mucus in adults and adolescents from 14 years of age.[15]

The upper and the lower respiratory tracts constitute a continuum, in particular with respect to the histological structure of the epithelium and of the secretory cells. There is parallelism in the pathologies of upper and lower airways:

Thus we find comparable symptoms of cellular inflammation with a predominance of eosinophilia in bronchial asthma and allergic rhinitis.

Likewise, there are analogies between acute and chronic bronchitis and rhinosinusitis, in which the neutrophilic inflammation is predominant.

Given the well-established use of acetylcysteine in bronchitis, it makes sense to pursue this therapeutic approach in rhinosinusitis as well. Indeed the first clinical investigations were reported more than 50 years ago. In a study of 32 sinusitis patients treated with a NAC solution administered by sinus irrigations, the authors concluded that NAC is an effective mucolytic agent (Komet et al.[16], 1965). About 20 years later Boner et al. (1984)[17] conducted a study in children for the treatment of sinusitis with NAC administered intramuscularly in combination with an antibiotic. In a publication by Zeiger (1992)[18] on “Prospects for ancillary treatment of sinusitis in the 1990s” the author stated that based on the apparent efficacy and relative safety of oral NAC in chronic bronchitis, “controlled” trials investigating its use in the treatment of chronic sinusitis should be encouraged. However also a more recently published phase 3 study in the indication of recurrent acute sinusitis did not meet the expectations for a recommendation of mucolytics in the current treatment guidelines for rhinosinusitis. This study, reported by Macchi et al. (2012)[19], employed only a single-blind design and NAC or the comparator substance were given in addition to the basic therapy of a nasal corticosteroid. Besides a very small sample size, a study reported by Bahtouee et al. (2017)[20] revealed even more weaknesses by adding NAC to amoxicillin-clavulanic acid, pseudoephedrine, and intranasal normal saline.

Hence to the best of our knowledge the proposed randomized controlled trial represents the first investigation to assess the efficacy and safety of NAC in rhinosinusitis according to current regulatory requirements.

6.4 Pharmacodynamic and Pharmacokinetic Properties

6.4.1 Pharmacodynamics

Data from the Summary of Product Characteristic (SmPC).[15]

Acetylcysteine is a derivative of the amino acid cysteine. The efficacy of acetylcysteine is secretolytic and secretomotoric in the area of the respiratory tract. It is discussed that it splits off the interconnecting disulphide bonds between the mycopolysaccharide chains and that it has a depolymerizing effect on DNA-chains (in purulent mucus). Due to these mechanisms, the viscosity of mucus should be reduced.

An alternative mechanism of acetylcysteine is meant to be based on the capacity of its reactive SH group to bind chemical radicals and to detoxify them in this way.

Furthermore, acetylcysteine contributes to an increase in glutathione synthesis, which is important for the detoxification of noxae. This provides the explanation for its antidotal effect in paracetamol intoxication.

A protective effect on the frequency and severity of bacterial exacerbations – when acetylcysteine is administered prophylactically - is described in patients with chronic bronchitis/mucoviscidosis.

6.4.2 Pharmacokinetics

Absorption[15]

Following oral administration, acetylcysteine is rapidly and almost completely absorbed and metabolized in the liver to cysteine, the pharmacologically active metabolite, as well as to diacetylcystine, cystine and further mixed disulphides.

Distribution[15]

Due to the high first-pass effect, the bioavailability of orally administered acetylcysteine is very low (approx. 10%). In humans, maximum plasma concentrations are achieved after 1-3 hours with the maximum plasma concentration of the metabolite cysteine in the range of approx. 2 µmol/l. The protein binding of acetylcysteine was determined to be about 50%.

Biotransformation[15]

Acetylcysteine and its metabolites occur in three different forms in the organism: partially in free form, partially bound to proteins via labile disulphide bonds and partially as incorporated amino acid. Acetylcysteine is excreted almost exclusively in the form of inactive metabolites (inorganic sulphates, diacetylcystine) via the kidneys. The plasma half-life of acetylcysteine is approximately 1 hour and is mainly determined by the rapid hepatic biotransformation. Impaired hepatic function therefore leads to prolonged plasma half-lives of up to 8 hours.

Elimination[15]

Pharmacokinetic studies with intravenous administration of acetylcysteine revealed a distribution volume of 0.47 l/kg (in total) or 0.59 l/kg (reduced); the plasma clearance was determined to be 0.11 l/h/kg (in total) and 0.84 l/h/kg (reduced), respectively. The elimination half-life after intravenous administration is 30-40 minutes while excretion follows three-phase kinetics (alpha, beta, and terminal gamma phase).

Acetylcysteine crosses the placenta and is detected in cord blood. No information is available regarding excretion into breast milk.

No knowledge is available concerning the behaviour of acetylcysteine at the blood-brain barrier in humans.

7 Trial Objectives

7.1 Primary Objective

The primary objective of the present trial is the assessment of 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.

7.2 Secondary Objectives

The secondary objective of the present trial is the assessment of safety and tolerability 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.

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.

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.

8.3 Benefit-Risk Evaluation

8.3.1 Adverse Drug Reactions Described in the SmPC of Acetylcysteine 600 mg effervescent tablet

Data from the Summary of Product Characteristic (SmPC)[15]

The evaluation of undesirable effects is based on the following information on frequencies:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data).

Immune system disorders	Uncommon Very rare	Hypersensitivity reactions Anaphylactic shock, anaphylactic / anaphylactoid reactions
Nervous system Disorders	Uncommon	Headache
Cardiac disorders	Uncommon	Tachycardia
Vascular disorders	Uncommon Very rare	Hypotension Hemorrhage
Respiratory, thoracic and mediastinal disorders tract	Rare	Dyspnea, bronchospasm – predominantly in patients with hyperreactive bronchial system in case of bronchial asthma
Gastrointestinal disorders	Uncommon Rare	Stomatitis, abdominal pain, nausea, vomiting, and Diarrhoea Dyspepsia
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, rash, angioedema, itching, exanthema
Ear and labyrinth disorders	Uncommon	Tinnitus
General disorders and administration site conditions	Uncommon Not known	Fever Facial enema

A very rare occurrence of serious skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in temporal association with the use of acetylcysteine. In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects.

In case of recurrence skin and mucosal lesions, medical advice should be sought at once and the use of acetylcysteine terminated immediately.

In addition, the occurrence of hemorrhages in association with the administration of acetylcysteine has very rarely been reported, partially with hypersensitivity reactions. A decreased blood platelet aggregation in the presence of acetylcysteine has been confirmed by various studies. The clinical relevance has not yet been clarified to date.

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.

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.

8.4.2.1 Other Conditions

Disease(s) present at screening (Visit 1) is regarded as **concomitant disease** and will be carefully documented in the CRF and assessed by the investigator in context of the exclusion/ withdrawal criteria listed in section 8.4.2.

Disease(s) occurred within the last 6 months and stopped prior to screening Visit 1 is regarded as **previous disease** and will be carefully documented in the CRF and assessed by the investigator in context of the exclusion/ withdrawal listed in section 8.4.2.

Disease(s) newly occurring during the trial (intercurrent disease) or any aggravation of a pre-existing (concomitant) disease will be regarded as Adverse Event (AE) and will be documented on the CRF pages for documentation of the concomitant disease(s) and in the AE form.

If medically required in respect of the patient's safety, the patient is to be withdrawn from the trial and the "protocol for termination of the trial" will be filled in by the investigator.

8.5 Trial Medication

8.5.1 Identity of Investigational Products

8.5.1.1 Test Product

Name:	Acetylcysteine 600 mg effervescent tablet[15]
Marketing authorization holder in Germany:	HEXAL AG
Marketing authorization No:	[redacted]
Formulation:	effervescent tablet
Active substance:	acetylcysteine
Excipients:	[redacted]
Strength:	600 mg acetylcysteine per effervescent tablet
Dosing schedule:	over 14 days **according to the randomized double-blind treatment** (*see randomization section*) (*please refer to 8.5.4)*
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]

8.5.1.2 Placebo to Test Product

Name:	Placebo
Formulation:	effervescent tablet
Active substance:	none
Excipients:	[redacted]
Strength:	none
Dosing schedule:	over 14 days **according to the randomized double-blind treatment** (*see randomization section*) (*for details please refer to 8.5.4*)
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]

8.5.2 IMP Administration and Duration of Treatment

Patients will undergo a screening visit (Visit 1) within one day prior to randomization (Visit 2 or baseline visit).

Patients who meet the inclusion/ no exclusion criteria will be randomized to one of the following double-blind treatment on Day 1 (Visit 2):

- Group A: 600 mg acetylcysteine: one tablet test product plus three tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR*
- Group B: 1200 mg acetylcysteine: two tablets test product plus two tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR*
- Group C: 2400 mg acetylcysteine: four tablets test product per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR*
- Group D: Placebo: four tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily).

The IMP treatment period will last for 14 days but in case of delayed final visit (Visit 6) the patient can voluntarily take reserve study medication for a maximum of 3 additional days. The double-blinded medication will be dispensed to the patients on Day 1 (Visit 2).

The route of administration of the trial medication is described in sections 8.5.1.1 and 8.5.1.2.

8.5.3 Packaging and Labelling

[redacted] (subcontracted by HEXAL AG) will pack and supply the trial medication together with sealed envelopes for unblinding in case of emergency.

Packaging, labelling and blinding will be according to GMP requirements, international and national laws and regulations.

The master labels will be prepared in English and translated into the respective local language(s).

[redacted] will ship the trial medication (in boxes of 4 patient kits inclusive emergency envelopes) to the respective central depot in the countries involved (*see below*).

Germany	[redacted] Contact person: [redacted] Phone.: mobile: Email:
Bulgaria	[redacted] Contact person: [redacted] mobile: email:
Russia	[redacted] Phone: Contact persons [redacted] Phone: (ext. Fax: mobile: E-mail: [redacted] Phone: (ext. Fax: mobile: Email:
Moldova	[redacted] Contact person: [redacted] mobile: Email:

The **randomized Patient Kit (box) carrying a tear-off label will include 14 Daily Kits** (numbered 1-14) and **one separate color-coded box with 3 Replacement/ Reserve Daily Kits** (numbered 1-3). The composition of one Patient Kit (box) is presented in TF 1.

Each **Daily Kit** and the **Replacement/Reserve Daily Kits** will contain 2 tablets for the morning intake and 2 tablets for the noon intake. The composition of one Daily Kit is presented in TF 2.

The Replacement medication (in case of lost or damaged IMP) or the Reserve medication (in case of delayed final visit will be provided for 3 days and the voluntary use of this reserve medication will be documented in the patient diary.

The Patient Kit (box) will be handed out to the patient on Visit 2 by the investigator.

PATIENT KIT for Randomization No.: .....

The Patient Kit is to be dispensed at Visit 2 and the tear-off label is to be affixed to the CRF

Folding box board
DAILY KIT 1
2 tablets for the morning intake in the **clinical site** and
2 tablets for the noon intake at home

Folding box board
DAILY KIT 4
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 7
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 10
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 2
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 5
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 8
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 11
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 3
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 6
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 9
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 12
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Replacement/Reserve Medication Box

Folding box board
REPLACEMENT/RESERVE KIT No. 1
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
REPLACEMENT/RESERVE KIT No. 2
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

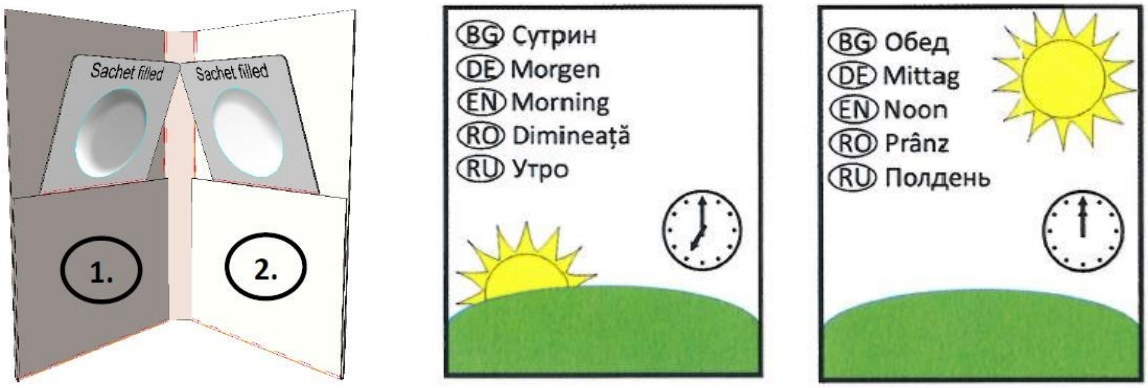
Folding box board
REPLACEMENT/RESERVE KIT No. 3
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

Folding box board
DAILY KIT 13
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

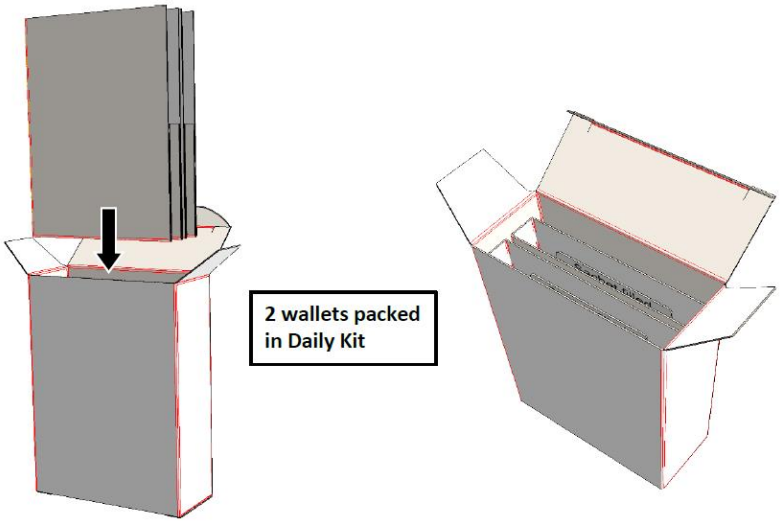
Folding box board
DAILY KIT 14
2 tablets for the morning intake at home + 2 tablets for the noon intake at home

TF 1 Composition of one patient kit

Upper panel: Wallet with 2 tablets (1 and 2) for one dose, labeled on the back side for morning or noon.



Lower panel: 2 wallets (for morning and noon dose) packed in one daily kit.



TF 2 Composition of one daily kit

8.5.4 Methods of Assigning Patients to Treatment Group

The trial medication will be pre-labelled in accordance with the randomization list (see section 10.6).

The patients will be assigned a unique per site 3-digit screening number reflecting the order in which screening took place at the clinical center.

At Visit 2 all patients eligible for randomization will be assigned a unique 4-digit randomization (patient) number, which is printed on the labels of IMP patient kits provided to centers. Patients will be randomized to the double-blind treatment in one of the following four treatment groups:

- Group A: 600 mg acetylcysteine: one tablet test product plus three tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR*
- Group B: 1200 mg acetylcysteine: two tablets test product plus two tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR*

- Group C: 2400 mg acetylcysteine: four tablets test product per day (to be taken as two tablets dissolved in a glass of water, twice daily) *OR*
- Group D: Placebo: four tablets placebo per day (to be taken as two tablets dissolved in a glass of water, twice daily).

The act of randomization is equivalent to assigning a randomization number to a patient during the **Visit 2 and the administration of the first dose of IMP**.

8.5.5 Blinding

The present trial will have a double-blind design for the whole duration of the trial (see section 10.6).

At Visit 1 the patients will receive a "Trial Identity Card" which needs to be carried along for any case of emergency.

The Test IMP and the Placebo will be identical in their appearance and the labels will not contain any information about the identity of the product.

The investigator will be held blind and will receive one set of sealed emergency envelopes for each patient. Another set will be stored at the sponsor's responsible pharmacovigilance function. The emergency envelopes contain information about the IMP identity according to the randomization schedule for each subject. The emergency envelope may only be opened in the case of necessary identification of the study medication.

The emergency envelopes of all treated patients will be kept in the ITF during the study. The state of all emergency envelopes will be checked by the CRAs at each regular monitoring visit.

Emergency unblinding of treatment assignment

In an emergency, the code for each separate subject can be opened to identify the treatment given to that subject. The code is not to be opened for any reason, other than an emergency where unblinding is required for the medical management of the patient. Where possible, the clinical research manager (Lek Pharmaceuticals d.d.) and the project manager(s) at [redacted] have to be contacted before breaking the blind for any patient.

When the investigator opens any individual code, he/ she must record the date and reason for breaking the code in the CRF. The investigator must also immediately inform the responsible persons, clinical research manager (Lek Pharmaceuticals d.d.) and the project manager(s) at [redacted] (see section 9.3.6).

Decoding by opening the emergency envelope leads to an immediate cessation of the trial for this patient but the subject should be followed until resolution of the (serious) adverse event.

After completion of the clinical part, sealed emergency envelopes will be returned to central depot(s) along with the unused trial medication.

8.5.6 Storage and IMP Accountability

HEXAL will supply the study centers *via* central depots with the study medication and demonstration samples. Shipments from the central depot to study centers and transfers back to the central depot will be documented on shipment forms including shipment date, patient number, visit number, batch number, quantity of study medication or demonstration samples, date received and method of shipment and will be confirmed by the investigator with his/her signature (or by signature of designated personnel). A copy of this receipt form must be kept by the investigator and another copy will be stored in the TMF at [redacted].

The investigator will be responsible for proper storage of the investigational medicinal products (IMPs) according to the temperature conditions printed on the medication labels, until the IMP dispensation to the patient.

The IMPs have to be stored in the clinical center(s) according to the sponsor's instruction printed on the labels.

All IMPs must be stored separately from all other hospital/ practice stocks, locked and only accessible for authorized study personnel. Temperature monitoring has to be performed by means of electronic device in the clinical center and the temperature records must be monitored by the local CRAs.

The trial medication will be provided by the sponsor in a sufficient quantity for the needs of the whole trial. The sponsor is responsible for keeping an appropriate amount of each trial medication to allow repeated pharmaceutical analysis.

The patients will receive the trial medication for the IMP intake at home and will be informed to store the medication according to the sponsor's instruction printed on the labels. The patients have to bring back on each visit the empty IMP packaging of used medication and the unused trial medication on Visit 6.

All IMPs must be accounted for at the end of the trial. It is not allowed to use the trial medication for any other purpose. The receipt, dispensation to the patient and return of trial medication is to be documented by the investigator in an IMP accountability form and is to be monitored by the local CRAs in the respective countries.

IMP destruction at the central depots or by a subcontracted company will be authorized by HEXAL/its representative. After completion of the destruction procedure the respective document(s) will be sent to the responsible Clinical Research Manager at Lek Pharmaceuticals d.d. for archiving in the TMF.

8.5.7 IMP Non-Conformances

1. DEFINITIONS

Non-conformances to the investigational medicinal product (Test product and Placebo) can include:

1) Complaints connected to the quality of the product such as
   - any fault of quality and/or effectiveness e.g. change of visual appearance, change of amount, damaged tablets/capsules, presence of foreign matter.
   - any fault of the containers and outer packages e.g. surface imperfection, container leakage, missing contents.
   - any fault of the labelling e.g. missing or illegible label.
   - any falsification of the medicinal product e.g. suspected product mix-up, tampering or counterfeiting.
2) Deviations connected to the transport of the product, such as damaged transport carton and/or damaged secondary package upon receipt of the shipment, missing drugs from the shipment package, unsuitable transport conditions.

2. PROCESS

In case any of the non-conformances listed above are detected or information about these non-conformances has been received, the completed Non-conformance Report must be sent to the sponsor/its representative within 24 hours.

In parallel, the local CRAs of the study must be informed about the non-conformance. If possible, a photo of affected material should be attached to the report. Affected material should be retained and stored according to the storage conditions label and/or returned to sponsor if requested by the sponsor/its representative.

8.5.8 Prior and Concomitant Medication, Therapeutic Measures

Any medication other than the IMPs (described in section 8.5.1) is defined as **concomitant medication**. Any concomitant medication will be carefully documented in the CRF specifying the substance (name of medication), reason for administration, administration scheme (regimen, no. of units, dose per unit) dosage form, route of administration, start and stop date of treatment or ongoing (if applicable) in context of the exclusion criteria listed in section 8.4.2.

The following **concomitant medication is NOT ALLOWED for the present trial**:

- Intranasal or systemic use of corticosteroids within 30 days prior to screening visit and during the trial;
- Intranasal or systemic use of antibiotics within 30 days prior to screening visit and during the trial;

- 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).

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

- physical examination per body system: general/nutritional sate, skin, head/neck, eyes, cardiovascular, respiratory, gastrointestinal, hepatic/biliary, endocrine/metabolic, lymph nodes, urogenital, neurological, psychiatric, musculoskeletal
- **ENT examination** of nose (septum, mucosa, secretion, obstruction, polyps), ears (effusion and erythema), and mouth/ throat (anterior and posterior discharge, dental abnormalities and halitosis)
- laboratory examination of blood (please see below)
- serum pregnancy test (hCG) for female subjects (please see below)
- check of inclusion criteria according to protocol
- check of exclusion criteria according to protocol
- investigator's decision on patient's enrolment.

The **blood specimen (30 mL) for the screening safety laboratory investigations** will include the following parameters:

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

The investigator will be provided with the original laboratory print-out(s) or certified copy (dated and signed by the laboratory staff) of the original laboratory print-out(s) for the individual patient health medical record file. The laboratory results have to be entered into the CRF. Any values out of range have to be assessed by the investigator as "not clinically relevant" (NCR) or "clinically relevant" (CR). For implausible laboratory values e.g. due to technical error or print-out error, the investigator will use the assessment "implausible value" (IPV).

If medically required, a separate blood draw will be taken for follow-up of CR or IPV parameters.

Serum pregnancy test (hCG) in all female patients. The result will be documented in the CRF. In case of a positive test result, this patient cannot be included in the trial.

All laboratory blood tests will be carried out in a certified local laboratory. A signed and dated list of the normal ranges and units of the laboratory blood and parameters and the certificate of the laboratory will be provided to [redacted] before the start of the trial. Also updates of the laboratory reference ranges/ certificates (if any) will be provided to [redacted].

VISIT 2 (Day 1 – between 7 and 9 a.m.)

The following procedures will be performed and documented in on this day:

- date and time of examination
- patient identification by means of national ID card or other national ID document
- 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
- documentation of any changes in the concomitant therapy(ies)/ medication(s) or use of other therapeutic measures/ actions
- adverse event questioning
- check of exclusion/withdrawal criteria and further patient eligibility
- **Major Symptom Score (MSS) assessment by the patient (transcribed by the investigator from TSSF into the CRF, and constituting the baseline value)**
- dispensation of the patient diary
- **SNOT-22 questionnaire on Day 1** (documented by patient in the diary during the visit in the clinical site)
- dispensation of a patient study identification card
- **Randomization to double-blind treatment**
  - **dispensation of the Patient Kit (box) containing the double-blinded trial medication for 14 days and including the separate Replacement/Reserve medication box with 3 Daily Kits**
  - **first intake of 2 tablets solved in 200 mL of water (morning dose of Daily Kit 1) in the presence of the investigator during the intake of breakfast. A pre-packed snack (e.g. croissant or similar) and a small beverage will be provided to the patient for breakfast.**
  - patient instructions for further intake of medication at home with the breakfast and lunch, for daily documentation of MSS in the diary and for correct storage of medication at home
  - patient instructions for return of the diary and the used medication at next visit for investigator's check.

VISIT 3 (Day 4)

The following procedures will be performed and documented in on this day:

- date and time of examination (visit)
- patient identification by means of national ID card or other national ID document
- 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
- documentation of any changes in the concomitant therapy(ies)/ medication(s) or use of other therapeutic measures/ actions
- adverse event questioning

- check of exclusion/ withdrawal criteria and further patient eligibility
- **review of the Patient Diary entries and compliance check; check of the correct documentation of Major Symptom Score (MSS) recorded by the patient once a day before intake of the morning dose**
- **detach the originals of the completed patient diary pages (top pages) and retain in the ITF until the final shipment of the complete diary to [redacted] for data entry in the clinical database**. **The no-carbon copy paper diary pages remain in the ITF of the clinical center.**
- assessment of the overall response to treatment (investigator)
- check of the returned used Daily Kits
- patient instructions for further intake of medication at home with the breakfast and lunch, for daily documentation of MSS and SNOT-22 (on Day 7) in the diary and for correct storage of medication at home
- patient instructions for return of the diary and the used medication at next visit for investigator's check.

VISIT 4 (Day 7)

The following procedures will be performed and documented in on this day:

- date and time of examination (visit)
- patient identification by means of national ID card or other national ID document
- 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
- documentation of any changes in the concomitant therapy(ies)/ medication(s) or use of other therapeutic measures/ actions
- adverse event questioning
- check of exclusion/withdrawal criteria and further patient eligibility
- **ENT examination** of nose (septum, mucosa, secretion, obstruction, polyps), ears (effusion and erythema), and mouth/ throat (anterior and posterior discharge, dental abnormalities and halitosis)
- **review of the Patient Diary entries and compliance check; check of the correct documentation of Major Symptom Score (MSS) recorded by the patient once a day before intake of the morning dose and check of the correct documentation of SNOT-22 questionnaire on Day 7** (by patient, in the diary)
- **detach the originals of the completed patient diary pages (top pages) and retain in the ITF until the final shipment of the complete diary to [redacted] for data entry in the clinical database**. **The no-carbon copy paper diary pages remain in the ITF of the clinical center.**
- assessment of the overall response to treatment (investigator)
- assessment of the overall tolerability (investigator and patient)
- check of the returned used Daily Kits

- patient instructions for further intake of medication at home with the breakfast and lunch, for daily documentation of MSS in the diary and for correct storage of medication at home
- patient instructions for return of the diary and the used medication at next visit for investigator's check.

VISIT 5 (Day 10)

The following procedures will be performed and documented in on this day:

- date and time of examination (visit)
- patient identification by means of national ID card or other national ID document
- 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
- documentation of any changes in the concomitant therapy(ies)/ medication(s) or use of other therapeutic measures/ actions
- adverse event questioning
- check of exclusion/ withdrawal criteria and further patient eligibility
- **review of the Patient Diary entries and compliance check; check of the correct documentation of Major Symptom Score (MSS) recorded by the patient once a day before intake of the morning dose**
- **detach the originals of the completed patient diary pages (top pages) and retain in the ITF until the final shipment of the complete diary to [redacted] for data entry in the clinical database. The no-carbon copy paper diary pages remain in the ITF of the clinical center.**
- assessment of the overall response to treatment (investigator)
- check of the returned used Daily Kits
- patient instructions for further intake of medication at home with the breakfast and lunch, for daily documentation of MSS and SNOT-22 (on Day 14) in the diary and for correct storage of medication at home
- patient instructions for return of the diary and the used medication at next visit for investigator's check.

END OF TREATMENT on Day 14

In case of delayed final visit (Visit 6), the patient can voluntarily take reserve study medication for a maximum of 3 additional days.

VISIT 6 (Day 15 (+3))

The following procedures will be performed and documented in on this day:

- date and time of examination (visit)
- patient identification by means of national ID card or other national ID document

- 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
- documentation of any changes in the concomitant therapy(ies)/ medication(s) or use of other therapeutic measures/ actions
- adverse event questioning
- physical examination per body system: general/nutritional state, skin, head/neck, eyes, cardiovascular, respiratory, gastrointestinal, hepatic/biliary, endocrine/metabolic, lymph nodes, urogenital, neurological, psychiatric, musculoskeletal
- **ENT examination** of nose (septum, mucosa, secretion, obstruction, polyps), ears (effusion and erythema), and mouth/ throat (anterior and posterior discharge, dental abnormalities and halitosis)
- laboratory examination of blood (please see below)
- serum pregnancy test (hCG) for female subjects (please see below)
- **review of the Patient Diary entries and compliance check; check of the correct documentation of Major Symptom Score (MSS) recorded by the patient once a day before intake of the morning dose and for the correct documentation of the last SNOT-22 questionnaire reported by the patient in the diary on Day 14**
- **detach the originals of the completed patient diary pages (top pages) and retain in the ITF until the final shipment of the complete diary to [redacted] for data entry in the clinical database**. **The no-carbon copy paper diary pages remain in the ITF of the clinical center.**
- **last Major Symptom Score (MSS) reported by the patient during the visit on Day 15(+3) and transcribed from TSSF by the investigator into the CRF**
- assessment of the overall response to treatment (investigator)
- assessment of the overall tolerability (investigator and patient)
- check of the returned used Daily Kits and the used or not used Replacement/Reserve Daily Kits (1, 2, 3).

The **blood specimen (30 mL) for the final safety laboratory investigations** will include the following parameters:

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

Serum pregnancy test (hCG) in all female patients.

The result will be documented in the CRF. **In case of a positive test result, the investigator must report it immediately (within 24 hours)** of awareness to the Country Patient Safety Head and in copy to the Study Managers (see 9.3.7).

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, inborn abnormalities, or maternal and/or newborn complications.

Any values out of range have to be assessed by the investigator as “not clinically relevant” (NCR) or “clinically relevant” (CR). For implausible laboratory values e.g. due to technical error or print-out error, the investigator will use the assessment “implausible value” (IPV). If medically required, a separate blood draw can be taken for follow-up of CR or IPV parameters.

FOLLOW-UP PHONE CALL (within 7 days after Visit 6 or earlier in case of premature termination)

- date of phone call
- check of adverse events after Visit 6.

During the phone call the investigator will check if any AE occurred after Visit 6 and if medically required the patient can be invited for additional (not trial related) visits. The results of these additional examinations and treatments will remain in the individual medical health records/ files of the clinical center(s) only. The date of the last follow up call of the last patient in the trial will be defined as the end of the trial.

In case that the investigator cannot reach the patient for the final follow-up call, he/she will document this in the CRF.

9.1 Trial Specific Efficacy Assessments

The following trial specific efficacy assessments will be performed by the PATIENT:

- **Major Symptom Score (MSS)**

The MSS combines the 5 most relevant symptoms of rhinosinusitis based on expert clinician recommendations[1, 21, 22] (**rhinorrhea/ anterior discharge, postnasal drip, nasal congestion, headache, and facial pain/pressure as reported by the group of Meltzer**[21] and Revicki et al.[22]) and has been employed as primary efficacy criterion in several clinical trials[1].

Assessment of symptom severity. The patient will rate the severity of each of the five symptoms of the MSS using a four-point rating scale of increasing severity (⓪ = none/not present, ① = mild, ② = moderate, ③ = severe).

The MSS will be assessed by the patient at screening (Visit 1) and immediately before randomization (Visit 2; this will constitute the baseline value). The investigator will transcribe both patient’s MSS assessments into the CRF.

Thereafter, the patient will document the MSS in the patient diary once a day before intake of the morning dose, starting with Day 2 until Day 14 (last day of treatment or earlier in case of drop-out).

The last MSS will be assessed by the patient during Visit 6 and transcribed into the CRF.

- **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.

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.

9.3.6 Emergency Unblinding for the Treatment of SAEs

The investigator should unblind the treatment (with the emergency envelope) for an individual case only in emergency situations, and only if relevant to the subsequent treatment of the subject (see also section 8.5.5 on unblinding).

9.3.7 Pregnancies

The investigator must report any cases of pregnancy of subjects in the course of a study **immediately (within 24 hours)** of awareness to the Country Patient Safety Head and in copy to the Study Managers (Sponsor/its representative and [redacted]), as described in section 9.3.5. **Pregnancies are only reported from the time of first IMP dose**.

The investigator should immediately withdraw the subject from the study, and should follow-up each case of pregnancy, and report the outcome, including spontaneous or voluntary termination, details of the birth, and any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Cases of pregnancy are reported on a “Drug Exposure in Pregnancy Form” (Novartis form). Pregnancy follow-up are reported on the same form, and should include an assessment of the relatedness of any untoward pregnancy outcome to the IMP.

Any SAE during pregnancy of a subject must be reported on the SAE Report Form and reported as described in section 9.3.5.

The investigator should retain a delivery confirmation of the “Drug Exposure in Pregnancy Form” for all recipients in the investigator study file.

For more detailed information refer to the “Quick Reference Guide for Completing the Drug Exposure in Pregnancy Form” (Novartis document).

9.3.8 IMP Related Complaints

In case of quality complaints related to the IMP, the investigator within 24 hours of learning of its occurrence informs the sponsor/its representative as described in section 9.3.5.

Any AE associated with a quality complaint needs to be documented and reported in addition by the investigator as described in section 9.3.4 and 9.3.5.

9.3.9 Special Case Scenarios

Special case scenarios can be serious or non-serious (see table below), and they should be reported like AE cases as described in section 9.3.4 and 9.3.5, even if no (other) AEs are associated with their occurrence.

Special case scenario	**Reportable within 24 hours from investigator to Country Patient Safety Head**
Drug exposure during breastfeeding	x
Intentional Overdose by patient (including suicide attempts, suicide attempt is always serious)	Only if associated with SAE
Drug / drug interactions	Only if associated with SAE
Withdrawal syndrome/ reaction	Only if associated with SAE
Drug dependence, misuse, abuse or addiction (always serious)	x
Suspected Transmission of infectious agents (always serious)	x
Death (incl. without other event, always serious)	x

9.3.10 Reconciliation

Reconciliation between the safety database of the sponsor and the clinical database at the CRO will be done periodically as described in a reconciliation plan (part of Data Management Plan generated by [redacted]) by comparing line listings from the safety database with the data in the clinical database.

The data management will review the CRFs / the clinical database for potentially unreported cases. For any reportable case, the following parameters need to match exactly between the clinical and the safety database: trial number, center number, subject/patient screening number, randomization number, investigational drug, seriousness, date of death (if applicable) and investigator causality. All other parameters only need to be plausibly and medically consistent. For any reportable case assessed as suspected or for other events of special interest (if applicable), a more detailed reconciliation should be conducted, including also treatment dates, outcome, medical history and concomitant therapy.

9.3.11 Investigator Training

By his/ her signature of the trial protocol, the principal investigator and the sub-investigator certifies that he/she has been trained in the Sponsor AE/SAE and pregnancy reporting obligations by the CRO as defined in the trial protocol.

9.3.12 Abnormal Clinical Laboratory Values

For abnormal clinical laboratory results the investigator must indicate in the CRF if the value is clinically relevant (CR) or not clinically relevant (NCR) or implausible (IPV).

Control laboratory investigations can be performed at any time during the trial. In case of unexplained or unexpected laboratory abnormalities with clinical relevance, the tests must be followed up until the results return to normal range or baseline value, and/ or adequate explanation for the abnormality is found. The results of control laboratory investigations must be documented in a separate CRF laboratory control page.

9.3.13 Safety Assessment

All patients screened and randomized in the trial will be included in the listing of safety data in the final study report. The reason for withdrawal and date of any withdrawal will be reported in the final study report. All adverse experiences will be listed and tabulated by severity, treatment and causal relationship to the IMP in final study report.

9.4 Premature Trial Discontinuation

The conditions for premature discontinuation of the trial in particular cases or in general are summarized below.

9.4.1 Withdrawal of Patients

Subjects may be withdrawn:

- at their own request with or without giving reasons,
- at the discretion of the investigator for reasons of medical prudence.

In either event, the sponsor/its representative will be immediately notified and the date and reasons for the withdrawal will be clearly stated in the patient's CRF.

Patients can also be withdrawn by the investigator for several reasons. These include:

- safety reasons
- if adverse event (including intercurrent disease) develop, which rule out continuation of the trial medication, or the AE could impair the validity of the results, or the AE makes further patient participation in this trial inadvisable,
- non-compliance,
- if circumstances, defined as withdrawal criteria are registered. Exclusion criteria defined in section 8.4.2 which are not present at screening but develop or are registered during the course of the trial are defined as withdrawal criteria.

For each patient withdrawn from the trial before the defined trial end, for whatever reason, a complete final examination must be performed as far as possible regarding the patient's availability and health condition. In case of withdrawal, the time, date and reasons for the withdrawal will be documented in the CRF.

9.4.2 Replacement of Drop-Outs

Drop-outs will not be replaced.

9.4.3 Premature Termination of the Trial

The sponsor/its representative may discontinue the trial at any time.

The ethics committees or the regulatory authorities involved might revoke their positive opinion regarding the trial which will lead to termination of the trial.

If, in the opinion of the coordinating investigator, the clinical observations in the trial suggest that it might not be justifiable for medical reasons to continue, he may terminate the trial after consultation with the sponsor/its representative or the sponsor/its representative may terminate the trial for safety, administrative or other reasons.

Reasons for discontinuation must be documented appropriately and provided to the sponsor/its representative, the ethics committees and regulatory authorities involved (if applicable).

The trial can also be terminated at single clinical center(s) due to any of the following reasons:

- on request of the center, or
- if results of an audit or regulatory inspection reveal critical findings which preclude further participation on the trial.

9.5 Data Quality Assurance

9.5.1 Monitoring

The sponsor will contract the monitoring of this clinical trial to [redacted] The monitoring visits in the present trial will be performed by [redacted] (for the centers in Germany) or its local subcontractors (see details in section 1.7).

A **Monitoring Plan** will be generated by [redacted] in accordance with [redacted] SOP 2406.

Monitoring of this study will be performed according to the standard operating procedures developed by [redacted] in order to check the adherence to the protocol in compliance with GCP guidelines and to ensure international acceptability of the study data. It is the responsibility of the investigator to assure that the study is conducted in accordance with the protocol, ICH-GCP and that valid data are entered into the CRF. Therefore, the investigator will make the records available to [redacted] or to the sponsor/its representative co-monitor

upon request at reasonable times. Case report forms will be checked by the CRA(s) for completeness and clarity.

Data verification is legally required and will be done by direct comparison with source documents in case of subject's respective consent or by cross-checking with source documents in the presence of the investigator - always giving due consideration to data protection and medical confidentiality. In this respect the investigator assures [redacted] to support at all times.

The investigator will permit representatives of [redacted] and the sponsor/its representative to monitor/co-monitor the study as frequently as necessary to determine that data recording and protocol adherence are satisfactory. The CRFs and related documents will be reviewed by the CRA(s) in detail in accordance with the [redacted] and the GCP regulation.

Visits may be conducted also by representative of [redacted] or the sponsor/its representative at suitable intervals throughout the study. These visits will be carried out for the purposes of verifying adherence to the protocol and the completeness and exactness of the data entered in the CRFs. The sponsor/its representative can have any information on the state of the study.

The original (top) pages of the CRF and the patient diary will be transferred to [redacted] after completion of the trial for the individual patient(s) for data entry in the clinical database. The transport of the completed CRFs/diaries to [redacted] will be organized in several shipments. The original CRF pages and the original patient diary pages (top page) will be transferred with the final clinical study report to the Sponsor/its representative. The no-carbon copy paper page (2nd page) of the CRFs and the diaries remain in the ITF at the clinical center.

It is the investigator's obligation to assure documentation of all relevant trial data in the subject's health medical file, such as medical history/concomitant diseases, date of study enrolment, visit dates, results of examinations, administrations of medication and AEs.

[redacted] will affirm and uphold the principle of the subject's right to protection against the invasion of privacy. Throughout the study, all data will only be identified by subject screening/ randomization number. The data will be kept blinded accordingly in all data analyses.

All obtained data will be checked for plausibility and completeness by the monitors and in-house by qualified staff of [redacted] Further plausibility checks will be performed by means of special computer programs. Study protocol and final report will be additionally reviewed by the sponsor/its representative.

9.5.2 Protocol Deviation Definition and Reporting

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol like missed evaluations, incorrect timing of evaluations, non-compliance with study medications and intake of medications not allowed or any non-adherence to the protocol that impacts patient’s rights, safety or welfare. After a patient has been enrolled, it is the investigator’s responsibility to make a reasonable effort to correct any protocol deviations and to continue the patient’s participation in the study. Protocol deviations do not themselves constitute a justification for withdrawal of a patient from the study (see section 9.4.3).

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation with the Sponsor/its

representative. Major deviations from the protocol will lead to the exclusion of a patient from the *Per Protocol Set* (PPS).

Protocol deviations will be reported to the project management of Lek Pharmaceuticals d.d. during the course of the study in the Monitoring Reports. The handling of these deviations will be defined in the Monitoring Plan.

All protocol deviations will be listed and the impact on the evaluability of the patients concerned will be discussed in the Blind Data Review meeting prior to database closure and any statistical analysis. Major Protocol Deviations leading to exclusion of patients from the per protocol analysis will be decided by the sponsor/its representative.

Protocol deviation notifications and reports are submitted to health authority and/ or relevant IEC/IRB according to applicable requirements/ guidelines/ law.

9.5.3 Data Management

The results from screening and data collected during the trial will be recorded in the CRF and in the patient diaries which will be designed and printed by [redacted]. Each CRF page will be signed and dated by the investigator.

All data concerning the study will be documented in the CRFs and patient diaries designed especially for this study and in data clarification forms issued by the data management.

The CRFs and patient diaries will consist of an original (1st page) and one second page (no-carbon copy paper). The 1st page will be sent to [redacted] for data entry in the clinical database. The no-carbon copy paper page will remain in the ITF of the clinical center.

SAE and Pregnancy forms will consist of one original only. The filled in SAE and/or Pregnancy reports should be submitted *via* fax or email to the Country Patient Safety Head and in copy to the Study Managers (Lek Pharmaceuticals d.d. [redacted]), as described in section 9.3.5 and the original document is filed in the ITF at the clinical center.

The Data Management Department of [redacted] will check the CRFs for completeness and plausibility (manually and computer-supported) and data clarification forms will be generated.

All corrections in the CRF are to be made legibly and signed by the investigator in accordance with GCP principles. All CRF pages (as described above) will be delivered thereafter to [redacted]. [redacted] is responsible for the first step of data validation, receiving the results from the investigator. Each subject will be identified in the database by the respective screening/ randomization number.

Description of the data entry procedure, the data handling (including data checks, coding of AEs, query procedure) and the software used for data management will be given in the Data Management Plan. Study specifics will be described in the Data Management Plan/ Data Validation Plan before the start of the data management process. The Data Management and Validation Report will be written after database closure.

The database for data capture will be created by [redacted] using Oracle Clinical 5.1.0 (or higher) for Oracle Database 12c & Oracle Thesaurus Management System 5.1.0 or higher. After locking the database, the files will be exported to SAS and handed over to the sponsor/its representative.

Regarding the data entry, a study specific data capture mask will be generated which allows a consecutive CRF-based data entry.

The data will be entered 2 times by 2 independent persons of the data management department (DMD). During the second data entry, the typist has to decide in case of discrepancies between both entries, which entry is correct. Concerning non-defined cases, the problem will be documented and clarified together with the data/project manager.

Each complete CRF input will be documented on a specific form (data management record). At the same time, the name of the data typist as well as date and daytime of each of the 2 data entries per CRF will be documented in the Oracle Clinical database.

After double data entry the data set will be checked for implausible entries, violations of inclusion/exclusion criteria, or other violations of the study protocol. After the data entry all data changes/additions or corrections will be documented on query forms according to GCP.

Coding of AEs, prior and concomitant medications and prior and concomitant diseases will be done according to last available versions of MedDRA (The Medical Dictionary for Regulatory Activities) and of WHO/ATC.

The data management and the statistical evaluation of the clinical study are done on a PC running Windows 10 operating system, using the statistical software package SAS, Version 9.4 (or higher).

9.5.4 Auditing

To guarantee that the performance of the trial is in accordance with the GCP provisions, in-house and, if needed, on-site audits may be carried out. The auditor will be independent from the staff involved in the proceedings of this trial.

The investigator agrees to give the auditor access to all relevant documents for review. The same applies in case of an inspection by authorities. In the case of any inspection of [redacted] by an authority the sponsor/its representative will be consulted before the inspectors are permitted access to any of the project records.

After each on-site audit the investigator will receive an audit confirmation by the auditor. This confirmation has to be filed together with the trial documentation and made available to the authorities in case of supervision. At the end of the trial, the audit certificate will be included in the final report.

9.5.5 Quality Assurance System

The [redacted] quality management department will conduct regular internal audits of the trial documents. A report will be prepared documenting the result of audits on the final trial protocol and related documents (e.g. CRF and patient information/ informed consent form) and the study report including appendices. A certificate confirming the audit performed will be included in the final study report.

10 Biometrics and Statistical Aspects

The biostatistical evaluation will be carried out by [redacted] by means of the statistical software package SAS for Windows (Statistical Analysis System, SAS-Institute, Cary NC, USA).

10.1 Statistical Analysis Plan

The statistical analysis plan (SAP) will be finalized prior to database lock. All relevant points related to the statistical analysis will be defined in the SAP. The main points are described in the following sections. In addition to these points the SAP will contain information on further topics (e.g., evaluation of baseline comparability of groups, different types of sensitivity analysis, handling of missing data, wrong treatment assignment, etc.).

10.2 Endpoints

10.2.1 Primary Endpoint

The primary endpoint is:

- Mean change from baseline in the daily MSS over the entire treatment period:

$$\frac{1}{14}\sum_{i=Day\ 2}^{Day\ 15}\left(x_i - x_{Day\ 1\ (baseline)}\right)$$

10.2.2 Secondary Endpoints

Secondary endpoints are:

- Time to onset of action defined as first day of active treatment on which MSS shows statistically significant difference from placebo
- MSS development over the course of the study
- SNOT-22 by visit and changes versus baseline
- Percentage of responders and non-responders to treatment based on the assessment of overall response to treatment by the investigator.

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.

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.

10.7 Data Presentation

The presentation of data will follow the ICH requirements for the structure and content of clinical study reports[6].

More details about the statistical analyses and the exact type of data presentation will be provided in the statistical analysis plan (SAP), which will be finalized prior to database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate.

There will be a clear accounting for all patients who entered the trial, using figures and tables in the text of the report. The numbers of patients who were randomized, and who completed the trial will be provided, as well as the reasons for all discontinuations, grouped by treatment and by major reason (lost to follow-up, adverse event, poor compliance etc.).

All important deviations related to trial inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be described. Protocol deviations will be appropriately summarized and grouped into different categories, e.g.:

- patients who entered the trial even though they did not satisfy the entry criteria
- patients who developed withdrawal criteria during the trial but were not withdrawn
- patients who received the wrong treatment or incorrect dose
- patients who received an excluded concomitant treatment.

All patients planned for inclusion in the statistical analysis will be allocated to the respective patient population, e.g., all patients receiving any investigational products, all patients with any efficacy observation, all patients completing the trial with a specified degree of compliance, etc.

The statistical analysis used will be described in the text of the report, with detailed documentation of statistical methods presented in appendix 16.1.9 of the study report. Important features of the analysis including the particular methods used, handling of drop-outs and missing data, adjustments for multiple comparisons, etc. will be discussed. Any changes in the analysis made after unblinding will be identified.

10.8 Interim Evaluation

No interim evaluation is planned for the trial.

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.

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.

11.6 Final Report

Prior to issuing the integrated final study report, [redacted] will prepare a draft report according to relevant ICH guidelines for approval by the sponsor/its representative. The draft report will be submitted to the QMD of [redacted], any findings will be considered in the final version.

11.7 Archiving

The investigator must maintain all trial essential documents as specified in ICH Topic E 6[3] and as required by the applicable regulatory requirement(s). The investigator/ institution must take measures to prevent accidental or premature destruction of and inadmissible access to these documents.

The investigator must make the [redacted] aware of the storage arrangements for the essential documents and conversely the [redacted] must inform the investigator/institution in writing of the need for record retention. The ultimate responsibility for the documents to be retained by the investigator/ institution resides with the investigator/institution.

[redacted] must obtain the investigator's/institution's agreement to retain the trial related essential documents until the [redacted] informs the investigator/ institution these documents are no longer needed. If the investigator becomes unable to be responsible for their essential documents (e.g. relocation, retirement etc.), [redacted] must be notified in writing of this change and informed as to whom the responsibility has been transferred.

Unless other law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical TMF/ ITF for at least 25 years after the end of the clinical trial.

The medical files of subjects should be retained in accordance with national legislation.

12 Qualification of the Investigator and Agreements

12.1 Qualification of the Coordinating Investigator, Principal Investigator and Sub-Investigator(s)

The coordinating investigator and the principal investigators must sign the protocol and any amendments. A signed and dated curriculum vitae (CV) showing the coordinating and principal investigator's qualification and more than two years of experience in the conduct of clinical trials will be submitted to the sponsor/its representative.

The investigator(s) must be qualified by education, language, training and experience to assume responsibility for the proper conduct of the trial. The investigators must meet all qualifications specified by the applicable regulatory requirements and must provide evidence of such qualifications throughout up-to-date curriculum vitae and/or other relevant documentation requested.

The investigators must be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, the current investigator's brochure, in the product information and other sources of information provided by the sponsor.

The investigators must be aware of and must comply with GCP and the applicable regulatory requirements.

The investigators must maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial related duties.

12.2 Agreements

12.2.1 Trial Initiation

The investigator or delegated staff **may not enroll any patients** (i.e. start any trial-related activities) prior to sending the approval of the IEC/IRB and, if applicable, the approval of the regulatory authorities, to the sponsor/its representative and prior to the completion of a trial initiation visit, conducted by a representative of [redacted] (local CRA).

The initiation visit will include an inventory of trial supplies and a detailed review/ explanation of the trial protocol and the CRF.

12.2.2 Confidentiality

All information concerning trial medication, all trial material and trial drug shall remain the property of the sponsor. [redacted] and the investigator are obliged to keep all data and information of the trial confidential and to use that data only after permission of the sponsor. It is understood that no trial material or information developed by the sponsor of this trial in connection with Acetylcysteine 600 mg effervescent tablet shall be made available to third parties, except for official representatives, such as regulatory health authorities.

Patients will be informed that all trial data will be stored on computer and handled strictly confidential. Patients will be identified throughout the documentation and evaluation procedures by the individual patient (screening/ randomization) number only, whereas all patient names will be kept secret by the investigator.

12.2.3 Investigator's Signature

By signing the trial protocol, the investigator takes responsibility that the trial is conducted according to the protocol, GCP and national drug laws and that the revised Declaration of Helsinki is observed in meaning and content to protect the participating persons.

12.2.4 Publication

Any scientific publication of study results requires the consent of the sponsor.

By signing the protocol, the investigator agrees that the trial results may be used for authorization purposes, for the compilation of information material and publication, including the statutory disclosure in publicly accessible databases, if applicable.

12.2.5 Investigator Fee

[redacted] (or its local representatives - CRO) and the investigator(s) will conclude an agreement on trial fees. This agreement will consider the number of patients that are to be included and costs differentiated by the visits performed for each patient and for laboratory analyses.

As this is a therapeutic trial the patients will receive remuneration of the traveling costs only and they are included in the investigator's fees.

13 References

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