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

STATISTICAL ANALYSIS PLAN

Version Final 2.0, date 07-Oct-2020

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2 Table of Contents

3 List of Abbreviations

ADAM	Analysis Data Model
AE	Adverse event
ANCOVA	Analysis of Covariances
[redacted]	[redacted]
CDISC	Clinical Data Interchange Standards Consortium
CEO	Chief Executive Officer
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of variation
DMD	Statistics and Data Management Department
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
GLM	General linear models (procedure in SAS)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IQR	Interquartile range
LOCF	Last Observation Carried Forward
MSE	Mean Sum of Squares of the error term (in ANCOVA)
MSS	Major Symptom Score
OC	ORACLE Clinical
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model
SNOT	Sino-Nasal Outcome Test (questionnaire)
SOP	Standard operating procedure
TLF	Tables, Listings, Figures
TSSF	Trial Specific Source Form
WHO	World Health Organization

Note: Not all of the above-mentioned abbreviations are used in this document.

4 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Trial Protocol.

The analyses described are based on the following trial documents:

- TRIAL PROTOCOL (Version Final 2.0, dated 24-Apr-2019) – ***GLOBAL as well as the latest country specific protocol versions as listed below*:**
  - TRIAL PROTOCOL AMENDMENT 1.0 (Version Final 1.0, dated 23-Aug-2019) with CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 1.0 (Version Final 3.0, dated 23-Aug-2019) - *Valid for Germany only*
  - TRIAL PROTOCOL AMENDMENT 2.0 (Version Final 1.0, dated 10-Sep-2019) with CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 2.0 (Version Final 4.0, dated 10-Sep-2019) - *Valid for Bulgaria and Moldova only*
  - TRIAL PROTOCOL AMENDMENT 3.0 (Version Final 1.0, dated 15-Oct-2019) with CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 3.0 (Version Final 5.0, dated 10-Oct-2019) - *Valid for Russia only*
  - TRIAL PROTOCOL AMENDMENT 4.0 (Version Final 1.0, dated 01-Nov-2019) with CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 4.0, (Version Final 6.0 dated 01-Nov-2019) - *Valid for Moldova only.*

Due to internal restructuring, all project management responsibilities for the clinical trial shifted with effective date 19-Aug-2020 from Sandoz Development Center (SDC) Holzkirchen with address Industriestraße 25 in 83607 Holzkirchen, Germany to Sandoz Development Center (SDC) Slovenia, Lek Pharmaceuticals d.d., Verovškova 57, 1526 Ljubljana, Slovenia. An amendment and new versions of the trial protocols valid for the four counties were generated (see below).

- **TRIAL PROTOCOL AMENDMENT 5.0 - GLOBAL (Version Final 1.0, dated 14-Aug-2020) *as well as the latest country specific protocol versions as listed below:***
  - CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 5.0 (Version Final 4.0, dated 14-Aug-2020) - *Valid for Germany only*
  - CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 5.0 (Version Final 5.0, dated 14-Aug-2020) - *Valid for Bulgaria only*
  - CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 5.0 (Version Final 6.0, dated 14-Aug-2020) - *Valid for Russia only*
  - CONSOLIDATED VERSION OF TRIAL PROTOCOL AFTER AMENDMENT 5.0, (Version Final 7.0 dated 14-Aug-2020) - *Valid for Moldova only.*

The following versions of the Case Report Forms and Patient Diary:

- CASE REPORT FORM (Version Final 5.0 dated 10-Sep-2019), issued AFTER AMENDMENT 2.0 - *Valid for Bulgaria only*
- CASE REPORT FORM (Version Final 6.0 dated 10-Oct-2019), issued AFTER AMENDMENT 3.0 - *Valid for Russia only*
- CASE REPORT FORM (Version Final 7.0 dated 01-Nov-2019), issued AFTER AMENDMENT 4.0 - *Valid for Moldova only*
- CASE REPORT FORM (Version Final 8.0 dated 28-Nov-2019) - *Valid for Germany only*
- PATIENT DIARY (Version Final 3.0, 26-Apr-2019)

- SOPs of CCDRD AG
- GUIDELINE FOR GOOD CLINICAL PRACTICE E6 (R2), Step 5, adopted by CHMP, 15-December-2016, issued as EMA/CHMP/ICH/135/1995
- ICH Topic E 9. Statistical Principles for Clinical Trials. Step 5. Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96). September 1998
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, EMA/CHMP/ICH/436221/2017, 17 February 2020

Further references are listed in section 9.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP Addendum.

5 General Study Information

5.1 Objectives

5.1.1 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.

5.1.2 Secondary Objective

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.

5.2 Study Design

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

5.3 Study Population

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

A detailed complete list of inclusion and exclusion/withdrawal criteria is shown in the (country specific) Trial Protocol in chapter 8.4.

5.4 Statistical Basis for 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 patients

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.

5.5 Randomization

Each of the patients will be randomly assigned to one of the following 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).

6 Definition of Endpoints

6.1 Primary Endpoint

The primary endpoint is the mean change from baseline in the daily Major Symptom Score (MSS) calculated as

$$\widehat{change}_{MSS} = \frac{1}{14} \sum_{i=Day\ 2}^{Day\ 15} \left(MSS_i - MSS_{Day\ 1\ (baseline)} \right),$$

The MSS will be assessed by the patient and documented in the patients' diaries (see section 7.4).

6.2 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.

6.3 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.

7 Statistical Analysis Conventions

7.1 Population for Analysis

7.1.1 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.

7.1.2 Full Analysis Set (FAS)

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.

7.1.3 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 (see Section 7.2.7) that could affect the efficacy evaluation, which include the availability of measurements of the primary endpoints. The latter will be prospectively defined before unblinding the trial.

7.2 Statistical Analysis Methods

7.2.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed.

Data will be described using summary statistics as described in the following sections. For qualitative variables frequency tables (with absolute numbers and percentages) will be created. For quantitative variables descriptive statistics (number of non-missing observations [n], arithmetic mean, standard deviation, median, minimum and maximum) will be calculated.

The standards used to support electronic data submission (e.g., clinic data, diagnostic lab data, efficacy data) will be based on the available version from the Clinical Data Interchange Standards Consortium (CDISC). The versions to be used during the course of this study will stay the same. The current versions are:

- Study Data Tabulation Model (SDTM) v1.6,
- Study Data Tabulation Model Implementation Guide (SDTM IG) v3.2,
- CDISC SDTM Controlled Terminology, 2019-09-27
- Analysis Data Model (ADaM) v2.1,
- Analysis Data Model Implementation Guide (ADaM IG) v1.1,
- The ADaM Basic Data Stucture for Time-to-Event Analyses v1.0
- ADaM Structure for Occurrence Data (OCCDS) v1.0
- CDISC ADaM Controlled Terminology, 2019-09-27
- Define-XML v2.0.

A Validation Report (using Pinnacle 21 Community, latest version) and respective Reviewer's Guides (Study Data Reviewers Guide and Analysis Data Reviewers Guide) will be prepared.

7.2.2 Rounding and Decimal Places

All raw data will be listed according to the number of decimal places presented in the source data (i.e. CRF, AE/SAE Report, SNOT diary).

In general, the following rules regarding summary statistics will be applied, unless otherwise stated:

- Mean and median will be tabulated to one more decimal place than the source data,
- Minimum and maximum will be tabulated to the same number of decimal places as the source data,

- Standard deviation will be tabulated to two more decimal places than the source data,
- Coefficient of variation (CV)%, if applicable will be presented to one decimal place.

The primary endpoint mean change will be rounded to 3 decimal places in listings and for further calculations (see section 7.4)

7.2.3 Statistical Significance Level

All statistical tests and comparisons are evaluated at the 5% significance level ($\alpha = 5\%$) if not stated otherwise.

7.2.4 Software

All statistical analysis will be performed using Statistical Analysis Software (SAS) Version 9.4 or higher.

7.2.5 Missing Data

In principle there will be no imputation of missing data.

For evaluation of the primary endpoint in the FAS population the last observation carried forward (LOCF) - principle will be applied.

If any patient 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, that means the last available post-baseline MSS (i.e. the respective rating of each of the symptoms) will be carried forward for the calculation of the mean change of the MSS.

For missing assessments of single symptoms which are missing between non-missing assessments, the same will be applied. I.e. the last non-missing score will be kept (which implies non-improvement).

With respect to the evaluation of the secondary endpoints in the FAS the following will be applied:

SNOT-22 score - in case of missing item values for the calculation of the score the worst item category will be used if not more than two item values are missing, otherwise the score will be regarded as missing.

Percentage of responders and non-responders: Missing values for the investigator's assessment of the overall response to treatment will be set to the worst case (1-major deterioration, i.e. considered as non-responder)

7.2.6 Interim Analysis

Not applicable.

7.2.7 Protocol Deviations

All protocol deviations will be listed by patient and will be discussed with the sponsor during the Blind Data Review Meeting before unblinding and database lock. Depending on the severity of protocol deviations (minor/major) the patients will be assigned to the respective statistical population.

Possible protocol deviations are discussed in a separate Protocol Deviation Management Plan.

The following categories of protocol deviations were defined in the Protocol Deviation Management Plan:

- Eligibility deviation,
- Withdrawal deviation
- Dosing deviation,
- Prohibited medication and therapies deviation
- Operational deviation

The final decisions regarding the severity of protocol deviations will be documented in a separate Protocol Deviation Report.

The occurred protocol deviations will be assessed by means of frequency tables, see Section 7.3.4.2.

7.3 Analysis Variables

7.3.1 Efficacy Variables

7.3.1.1 Major Symptom Score (MSS)

The MSS combines the following symptoms of rhinosinusitis based on expert clinician recommendations

- rhinorrhea/ anterior discharge,
- postnasal drip,
- nasal congestion,
- headache, and
- facial pain/pressure.

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 is then the sum of the single ratings.

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 from TSSF 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 from TSSF into the CRF.

Statistical evaluation of the MSS is described in section 7.4.

7.3.1.2 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.

All individual SNOT questionnaire results of the Safety Set will be listed by patient. Further statistical evaluation is described in section 7.4.2.

7.3.1.3 Investigator's Assessment of the Overall Response to Treatment

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

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.

All individual assessments of overall response of the Safety Set will be listed by patient. Further statistical evaluation is described in section 7.4.2

7.3.2 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Date of birth (in Germany only the year of birth will be recorded)
- Age in years at date of informed consent (derived, whereas age for patients from Germany cannot be derived exactly from the CRF, Discrepancy Clarification Forms will be used to obtain the age of the patients from the investigator)
- Ethnicity (Caucasian, Hispanic, Black, Asian, Unknown or other)
- Gender/ Sex
- Height without shoes (cm)
- Body weight inclusive indoor clothing without shoes (kg)
- Body mass index (BMI) calculated as [weight/height²] (kg/m²)
- Life Style and Habits (alcohol consumption, smoking status and drug abuse history)
- Anamnestic information (last participation in any clinical trial, allergies, …)
- Anamnesis on Acute Uncomplicated Rhinosinusitis
- Method of contraception (additional anamnesis for female patients only)
- Medical and surgical history (including previous and concomitant diseases)
- Previous medication (drug history)/ therapies (within 6 months prior to screening which stopped before screening)
- Concomitant medication (recorded at screening visit and/or during the trial)
- Medical or therapeutic measures (recorded at screening visit and/or during the trial)

All demographic data and background variables of the Safety Set will be listed by patient, except for the anamnestic information. The anamnestic information is only collected in order to document the eligibility of the patients. Additionally, demographic data of the patients which were only screened but not treated will be listed by patient.

Descriptive statistics for the quantitative data (age, height, weight, BMI) and absolute and relative frequencies of the quantitative data (sex, ethnic group) will be presented for the safety set, the FAS and for the PPS.

The concomitant medication (drug name, indication, administration scheme, dosage form, route of administration, start date and end date of medication) will be listed by patient. The end date will be substituted by the term 'ongoing' if the medication did not stop before termination of the trial. The listings contain the WHO Drug B3 coding up to level 4 for the used drugs, as well as MedDRA (Version 22.1 or higher) for the respective indications.

Frequency tables will be presented for medical and surgical history (including previous and concomitant diseases) and for the previous and concomitant medication.

The medical history will be displayed as incidences (number of findings and number of patients affected) for diseases and surgery which ended before start of the trial (Visit 2) by SOC, PT and treatment group for the safety set.

The concomitant diseases will be displayed as incidences (number of findings and number of patients affected) for diseases and surgery which are present at start of the trial (Visit 2) SOC, PT and treatment group for the safety set.

The previous medication, i.e. medication which stopped before the start of the trial (Visit 2) will be tabulated as numbers of findings and numbers of patients affected by WHO Drug B3 term Level 3, Preferred Name and by treatment group for the safety set.

The concomitant medication which is present at the start of the trial (Visit 2) and which starts during the trial, will be tabulated as numbers of findings and numbers of patients affected by WHO Drug B3 term Level 3, Preferred Name and by treatment group for the safety set.

7.3.3 Safety Variables

All evaluations of the safety variables will be performed in Safety Set.

7.3.3.1 Adverse Events

An **adverse event or adverse experience (AE)** is any untoward medical occurrence in a patient or clinical investigation patient 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), symptom, or disease temporally associated with the use of a medical product, whether or not considered related to the medical product.

Existing concomitant diseases are not considered AEs, except if they have worsened/adversely progressed during the study.

The Medical Dictionary for Regulatory Activities (MedDRA, Version 22.1 or higher) is used for coding adverse events.

All AEs with start date/time prior to first intake of IMP are pre-treatment AEs and will be assigned to screening.

Any adverse events with missing start date/time or the end date/time are treated as follows:

- If the date is known but the time is unknown, the time will be imputed with a time 0:00 h for the start and with 23:59 for the end. In the listings the unknown time will be displayed as NK. If the start date is a treatment date, then the AE will be assigned to the treatment of that date.
- If the start date is incomplete:
  - Missing day: will be imputed with the 1st of the month unless month is the same month of first dose of study drug; then it will be imputed with first dose date
  - Missing day and month: will be imputed with 1st January unless year is the same as first dose date; then it will be imputed with first dose date
  - Completely missing: impute first dose date unless the end date suggests it could have started prior to this in which case the 1st January of the same year will be imputed as the start date
- If the end date is incomplete:
  - Missing day: will be imputed with the last day of the month unless month is same as month of first dose of study drug; then it will be imputed with the last dose date
  - Missing day and month: will be imputed with 31st December unless year is the same as first dose date; then it will be imputed with last dose date
  - Completely missing (and not ONGOING): if the AE started prior to 1st dose date then it will be imputed the 1st dose date. If the AE started after 1st dose date then it will be imputed with the last dose date

The pre-treatment adverse events which occurred before intake of the first dose of IMP (between screening visit (Visit 1) on Day -1 and Visit 2 on Day 1) will be presented in listings.

The adverse events will be analyzed by means of frequency tables. For an overview a frequency table with numbers of patients affected will be presented by treatment for the categories (Summary of adverse events): total, adverse events leading to discontinuation, serious adverse events, and (serious) adverse events with outcome death.

Further frequency tables will be classified by system organ class (SOC), preferred term (PT) derived from MedDRA and by treatment. The numbers of adverse events as well as the numbers of patients affected will be presented.

Moreover, tables for incidences of adverse events and patients with respect to the following parameters will be created:

- Severity (mild, moderate, severe),
- Relationship between study medication and adverse event (suspected, not suspected),
- Outcome (not recovered / not resolved / unchanged; recovered / resolved, improving/ recovering/ resolving; recovered with sequelae; fatal; condition deteriorating; unknown).

All adverse events will be listed, these listings will be split into three parts containing the following columns:

Part I: Rnd. No. , Report No., Observed AE (in verbatim), Seriousness, Action taken with IMP; Severity, Outcome, Relationship to IMP, Relationship to NIMP

The report number is an identifier for the single adverse events within one patient (chronologically).

This part I will be displayed in two versions:

- first version is sorted by treatment group (where pre-treatment adverse events will be pooled as additional group), random number and report number,
- in the second version the adverse events are sorted by random number and report number.

The second and third part will only be displayed sorted by random number and report number with the following information:

Part II: Rnd. No., Report No., MedDRA Coding: Preferred Term (with Code), Date/Time of onset, Date/Time of end, Last date/time of dose before onset, Last treatment.

Part III: Rnd. No, Report No, Event treatment, Specification of event treatment.

These adverse events will be listed for the safety set. If patients experience adverse events who were not randomized, or had no intake of IMP then further listing for these events will be displayed.

7.3.3.2 Serious Adverse Events

A serious adverse event (SAE) or serious adverse reaction (SAR) 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, or
- 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.

The serious adverse events will be presented in listings.

7.3.3.3 Assessment of Tolerability

The tolerability will be assessed by the investigator and by the patient at Visit 4 and Visit 6. It is rated using a five-point rating scale: ① = very poor, ② = poor, ③ = medium, ④ = good, ⑤ = very good.

The assessments will be listed by patient.

The results will be presented by means of frequency tables by visit and treatment.

7.3.3.4 Vital Signs

The following vital sign measurements will be obtained according to the schedule of assessments in chapter 9 of the Trial Protocol on each visit and evaluated as normal or abnormal and judged regarding clinical relevance

- Blood pressure, systolic and diastolic [mmHg]
- Pulse rate [beats/min]
- Body temperature [°C]

The vital signs will be listed by patient.

A separate listing for only abnormal results including the assessment of clinical relevance will be presented.

Descriptive statistics for the values and for individual changes (absolute changes) to the baseline (measurement from screening visit) will be presented by measuring time point, parameter and treatment.

7.3.3.5 Physical Examination

A physical examination is performed at the entry and final examination per body system (general state; nutritional state; skin; head, neck; eyes; cardiovascular; respiratory; gastrointestinal; hepatic, biliary; endocrine, metabolic; lymph nodes; urogenital; neurological; psychiatric; musculoskeletal)

The findings, if any, will be listed by patient, abnormal findings will be listed separately.

The results for the examination by body system (normal, abnormal) and for the changes from entry to final will be presented by means of frequency tables. The changes will be displayed as shift for Visit 6 against Visit 1.

7.3.3.6 Examination of Nose, Ears, Mouth / Throat (ENT)

An examination of Nose (septum, mucosa, secretion, obstruction, polyps), Ears (effusion and erythema) and Mouth/Throat (anterior and posterior discharge, dental abnormalities and halitosis) will be performed at screening (Visit 1), at Visit 4 and at Visit 6.

The results will be listed by patient. The results per item and the findings (normal/abnormal) per system will be presented by means of frequency tables. The changes will be displayed as shift tables for Visit 4 against Visit 1 and for Visit 6 against Visit 1.

7.3.3.7 Safety Laboratory Examination

The safety laboratory examination will be performed at Visit 1 (screening) and Visit 6 (end of treatment) 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

The individual values of the clinical laboratory tests (hematology, blood chemistry) will be listed by patient.

Out-of-range values are marked with an assessment of clinical relevance (NCR = not clinically relevant, CR = clinically relevant). The course of out-of-range values is listed separately.

Descriptive statistics for each parameter will be presented by visit and treatment. Further descriptive statistics for individual changes (from Visit 1 to Visit 6) will be presented by treatment.

Frequency tables for the assessment of clinical relevance (normal, abnormal NCR, abnormal CR) will be presented by treatment. The changes of the assessment will be displayed as shift tables from Visit 1 to Visit 6.

In addition, a serum pregnancy test in all female patients is performed at Visit 1 and Visit 6. The results will be listed by patient.

7.3.4 Compliance of patients

7.3.4.1 Disposition of patients

The number of patients per site are presented by treatment group and population for analysis (screened, safety set, FAS, PPS).

The disposition of patients according to their presence at the corresponding visit (performed, not-performed, drop-out) will be presented by means of frequency tables by treatment group.

The documented main reason for drop-out (adverse event, inclusion criteria not met, exclusion criteria met, non-compliance, on patient's request, contact to patient lost or other) will be presented by means of frequency tables by treatment group.

7.3.4.2 Protocol deviations

The protocol deviations will be summarized by means of frequency tables by treatment group with respect to the category (eligibility deviation, withdrawal deviation, dosing deviation, prohibited medication deviation, operational deviation) and the assessment (minor/major).

7.3.4.3 Compliance with IMP

The dispensation and return of IMPs is documented by the investigator in the Study Medication Logbook, which is part of each patients' CRF. The daily intake of the IMPs (in the morning and at noon) is documented by the patients in their diaries.

In total it is expected that each patient takes 56 of the dispensed tablets (14 days, 2 tablets in the morning and 2 tablets at noon each day).

Compliance (in %) will therefore be calculated as the number of tablets which were taken, as documented in the diary, divided by 56.

Further the ratio of returned (not used) tablets to dispensed tablets will be assessed as a measure of drug accountability.

These measures of compliance and drug accountability will be analyzed descriptively with mean, standard deviation, minimum and maximum by treatment group.

7.3.4.4 Treatment duration and time intervals between visits

The total duration of treatment will be calculated as the number of days between first and last intake of the IMP; these dates are documented in the CRF as start of treatment (date and time) and end of treatment (date and time).

$$duration = date\ of\ end\ of\ treatment - date\ of\ start\ of\ treatment + 1$$

This duration will be analyzed descriptively (mean, standard deviation, minimum and maximum) by treatment group for the safety set, the FAS and the PPS.

The time intervals between Visit 1 and Visit 2, Visit 2 and Visit 3, Visit 2 and Visit 4, Visit 2 and Visit 5 and between Visit 2 and Visit 6 will be assessed descriptively (mean, standard deviation, minimum and maximum) by treatment group for the safety set, the FAS and the PPS.

The start of treatment (month and year) is analyzed by means of frequency tables by treatment group for the safety set.

7.4 Statistical Analysis of the Endpoints

7.4.1 Statistical Analysis of the Primary Endpoint

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 $\alpha = 0.05$ (two-sided) until the first non-rejection. No error rate adjustment is required.

The set of hypotheses is as follows:

$$H_{01}: \mu_A = \mu_D \text{ versus } H_{11}: \mu_A \neq \mu_D,$$

$$H_{02}: \mu_B = \mu_D \text{ versus } H_{12}: \mu_B \neq \mu_D,$$

$$H_{03}: \mu_C = \mu_D \text{ versus } H_{13}: \mu_C \neq \mu_D.$$

Where μ_{group} denotes “mean change from baseline in the daily MSS over the entire treatment period” in treatment group (Group A, B, C or D) for the respective strength.

Superiority of the Test treatment over placebo (PL) is confirmed if the p-value is below 5% and a positive treatment effect is shown.

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

The SAS procedure PROC GLM will be used for that purpose.

Basically, the following code will be used:

```
proc glm data=primary;
class treatment center;
model mss=treatment center baseline_mss;
estimate 'Group X vs D' treatment 1 -1 ;
where treatment='X' or treatment='D';
run;
```

The analysis will be performed for each hypothesis separately, i.e. only data of one active treatment group and the placebo group are included for the respective comparison.

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.

7.4.2 Statistical Analysis of the Secondary Endpoints

7.4.2.1 Time to onset of action defined as first day of active treatment on

which MSS shows statistically significant difference from placebo

This endpoint will be determined as follows:

For each day of assessment (Day 2 until Day 14) of MSS a two-sample t-test (by means of an ANCOVA with factors treatment, center and baseline MSS as covariate) comparing the mean MSS in one active treatment group versus placebo group will be performed. The following hypotheses will be tested:

$H_{0,g,v}: MSS_{g,v} = MSS_{D,v}$ vs. $H_{1,g,v}: MSS_{g,v} \neq MSS_{D,v}$

For the active treatment groups g (Groups A, B or C) and visits v (from Day 2 to Day 14).

For each hypothesis to test only the data related to the hypothesis will be used.

The earliest day showing a significant difference at level $\alpha = 5\%$ will then be defined as the time to onset of action.

This analysis is deemed to be descriptive and will be performed in FAS and in the PPS.

7.4.2.2 MSS development over the course of the study

For each day of assessment (Day 1 until Day 15, or up to 3 days later) descriptive statistics (mean, standard deviation, median, minimum and maximum) for the MSS per treatment group will be determined and displayed for the FAS and the PPS.

The mean values will be presented in a graphic containing the curves for all four treatment groups.

7.4.2.3 SNOT-22 by visit and changes versus baseline

The total scores (sum of all single assessments per subject) will be analyzed descriptively by treatment group and assessment day (Day 1 - Baseline, Day 7 and Day 14).

The change versus baseline will be determined individually as

$$change_{SNOT,day} = \frac{SNOT_{day} - SNOT_{baseline}}{SNOT_{baseline}} * 100\%,$$

where $SNOT_{day}$ denotes the SNOT Score on Day 7 or Day 14.

The percent change will be analyzed descriptively by treatment group and visit for the FAS and the PPS.

The mean SNOT values by treatment and visit will be presented in a graphic containing the curves for all four treatment groups.

7.4.2.4 Percentage of responders and non-responders to treatment based on

the assessment of overall response to treatment by the investigator

Based on the assessment of overall response responders are defined as patients who were cured by the treatment, i.e. with ratings 4 (minor improvement) and 5 (major improvement).

Accordingly, patients whose disease was unchanged or deteriorated, i.e. with rating 1 (major deterioration), 2 (minor deterioration) and 3 (no change) are defined as non-responders.

The mean percentages per treatment group and visit are presented. Differences between the active treatment groups and the placebo group will be investigated by means of two sided Chi-square tests (at significance level 5%) in the FAS and in the PPS.

The SAS procedure PROC FREQ with basically the following code will be used:

```
proc freq data=responders;
   tables treatment*response /chisq;
   where treatment='X' or treatment='D';
run;
```

For the group of non-responders frequency tables for month of inclusion and country will be displayed.

Additionally a Mantel-Haenszel will be performed using the month of inclusion as third control variable. This test is considered as sensitivity analysis to rule out the possibility that patients with seasonal rhinitis have an impact on the result.

The SAS procedure PROC FREQ with basically the following code will be used:

```
proc freq data=responders;
   tables incl_month*treatment*response /cmh;
   where treatment='X' or treatment='D';
run;
```

This sensitivity analysis will be performed in the FAS and in the PPS.

Bar charts of the relative number of the responders will be created per treatment group and by visit (Day 1, Day 7 and Day 14).

8 List of Tables, Listings and Figures

8.1 Tables to be included in the Clinical Study Report (Chapter 14)

Section	Table titles
14.1 Demographic data	Numbers of patients per site by analysis population
	Randomization list, safety set
	Documented reason for drop-out, safety set
	Disposition of patients, safety set
	Start of treatment, safety set
	Treatment duration, safety set
	Treatment duration, FAS
	Treatment duration PPS
	Time intervals between Visit 2 and all other visits, safety set
	Time intervals between Visit 2 and all other visits, FAS
	Time intervals between Visit 2 and all other visits, PPS
	Compliance with IMP, safety set
	Occurrence of protocol deviations, safety set
	Medical history - Diseases, surgeries which ended before start of treatment (Visit 2) by SOC, PT and treatment, safety set
	Concomitant diseases which are present at start of treatment (Visit 2) by SOC, PT and treatment, safety set
	Previous medication (ended before start of treatment, Visit 2) incidences by WHO Drug B3 term level 3, Preferred Name and treatment, safety set
	Concomitant medication (at start of treatment, Visit 2) incidences by WHO Drug B3 term level 3, Preferred Name and treatment, safety set
	Summary of demographic data, safety set
	Summary of demographic data, FAS
	Summary of demographic data, PPS

14.2 Efficacy data	Evaluation of the primary endpoint - Mean change from baseline in daily MSS ANCOVA and superiority test, Treatment A vs D, FAS Evaluation of the primary endpoint - Mean change from baseline in daily MSS ANCOVA and superiority test, Treatment A vs D, PPS Evaluation of the primary endpoint - Mean change from baseline in daily MSS ANCOVA and superiority test, Treatment B vs D, FAS Evaluation of the primary endpoint - Mean change from baseline in daily MSS ANCOVA and superiority test, Treatment B vs D, PPS Evaluation of the primary endpoint - Mean change from baseline in daily MSS ANCOVA and superiority test, Treatment C vs D, FAS Evaluation of the primary endpoint - Mean change from baseline in daily MSS ANCOVA and superiority test, Treatment C vs D, PPS Evaluation of secondary endpoint - Time to onset of action, FAS Evaluation of secondary endpoint - Time to onset of action, PPS Evaluation of secondary endpoint - MSS development of the course of the study, FAS Evaluation of secondary endpoint - MSS development of the course of the study, PPS Evaluation of secondary endpoint - SNOT-22 by visit and change to baseline, FAS Evaluation of secondary endpoint - SNOT-22 by visit and change to baseline, PPS Evaluation of secondary endpoint - Percentage of responders and non-responders, FAS Evaluation of secondary endpoint - Percentage of responders and non-responders, PPS Frequency table for month of inclusion and country in the group of non-responders, FAS Sensitivity analysis - Percentage of responders and non-responders controlled by month of inclusion, FAS Sensitivity analysis - Percentage of responders and non-responders controlled by month of inclusion, PPS

14.3 Safety	Vital signs - Descriptive statistics by treatment and visit, safety set Vital signs - Descriptive statistics of individual changes to baseline by treatment and visit, safety set Findings in the physical examination by treatment and visit, safety set Examination of ENT by treatment and visit, safety set Safety laboratory, hematology -Descriptive statistics by treatment and visit, safety set Safety Laboratory, hematology- Value classification by treatment and visit, safety set Safety laboratory, hematology - Changes in the value classification (entry to final) by treatment, safety set Safety laboratory, blood chemistry - Descriptive statistics by treatment and visit, safety set Safety laboratory, blood chemistry - Value classification by treatment and visit, safety set Safety laboratory, blood chemistry - Changes in the value classification (entry to final) by treatment, safety set
14.3.1 Adverse Events (per treatment / per patient)	Summary of adverse events, safety set Listing of pre-treatment adverse events, safety set Listing of serious adverse events, safety set Numbers of patients with adverse events by SOC, PT and treatment, safety set Incidence of adverse events by SOC, PT and treatment, safety set Numbers of patients with adverse events by SOC, PT, treatment and severity, safety set Incidence of adverse events by SOC, PT, treatment and severity, safety set Numbers of patients with adverse events by SOC, PT, treatment and causality, safety set Incidence of treatment events by SOC, PT, treatment and causality, safety set Numbers of patients with adverse events by SOC, PT, treatment and outcome, safety set Incidence of adverse events by SOC, PT, treatment and outcome, safety set

14.3.2 Abnormalities in Vital Signs, Laboratory, Physical Examination, etc.	Abnormalities in vital signs, safety set Abnormalities in physical Examination, safety set Abnormalities in ENT examination, safety set Time course of laboratory test results out of reference range, blood chemistry, safety set Time course of laboratory test results out of reference range, hematology, safety set

8.2 Figures to be included in the Clinical Study Report

MSS development of the course of study, mean curves, Full Analysis Set

MSS development of the course of study, mean curves, Per-Protocol Set

SNOT development of the course of study, mean curves, Full Analysis Set

SNOT development of the course of study, mean curves, Per-Protocol Set

Percentage of responders - bar charts by visit and treatment group, Full Analysis Set

Percentage of responders - bar charts by visit and treatment group, Per-Protocol Set

8.3 Listings (Appendix 16.2 of the Clinical Study Report)

Section	Table titles
16.2.1 Discontinued patients	Patients not treated with trial medication (only screened) Listing of drop-outs (withdrawal criteria / premature discontinuation), randomized and treated patients Disposition of patients treated with trial medication per study phase Inclusion criteria not met Exclusion criteria met
16.2.2 Protocol deviations	Protocol deviations
16.2.3 Patients excluded from the efficacy analysis	Patients excluded from the efficacy analysis (Per Protocol Set) Patients excluded from the efficacy analysis (Full Analysis Set)
16.2.4 Demographic data	Demographic data of patients treated with trial medication

Section	Table titles
	Demographic data of patients not treated with trial medication
	Life style and habits - Alcohol consumption, safety set
	Life style and habits - History of drug abuse or use of illegal drugs, safety set
	Life style and habits - Smoking status, safety set
	Anamnesis on acute uncomplicated rhinosinusitis, Major Symptom Score, safety set
	Medical and surgical history, safety set
	Previous medication, safety set
	Concomitant medication, safety set
	Medical or other therapeutic measures, safety set
	Method of contraception, safety set
	Vital signs, safety set
	Physical examination, safety set
	ENT examination, safety set
	Assessment of tolerability by patient, safety set
	Assessment of tolerability by investigator, safety set
16.2.5 Compliance and / or drug concentration data	Visit dates, safety set
	Dispensation of blinded medication
	Return and check of used blinded medication
16.2.6 Individual efficacy response data	Major Symptom Score (MSS) assessed by the patient
	Sino-nasal outcome test (SNOT-22) assessed by the patient
	Assessment of overall response to treatment by the investigator
16.2.7 Adverse event listings	Display of adverse events, part I, sorted by treatment group, safety set
	Display of adverse events, part I, safety
	Display of adverse events, part II, safety set
	Display of adverse events, part III, safety set (Specification of Event treatment)

Section	Table titles
	Display of serious adverse events, part I, safety set Display of serious adverse events, part II, safety set Display of serious adverse events, part III, safety set (Specification of event treatment)
16.2.8 Listing of Individual Laboratory Measurements by Patient	Laboratory test results - Abbreviation of test codes Laboratory test results of blood chemistry, safety set Laboratory test results of hematology, safety set Serum pregnancy test, safety set

9 Reference List

[1] Jund R, Mondigler M, Stammer H, Stierna P, Bachert C. Herbal drug BNO 1016 is safe and effective in the treatment of acute viral rhinosinusitis. Acta Otolaryngol. 2015 Jan;**135**(1):42-50