Statistical Analysis Plan

Document code: **TE_003_ANG_LSP_TSAP**

Trial code:	TE_003_ANG_LSP / NCT03095508
Trial title:	A Prospective, Multicenter, Open, Randomized, Parallel Clinical Trial for Comparative Assessment of Efficacy and Safety of Angal S, Topical Spray [Menthol], 0.5 mg + 2 mg/1 ml (Sandoz d.d., Slovenia), and ANTI-ANGIN® FORMULA, Topical Metered Spray, 0.12 mg + 0.24 mg/dose (OOO Valeant, Russia) in Treatment of Patients with Uncomplicated, Acute, Infectious and Inflammatory Diseases of the Pharynx Accompanied by a Sore Throat
Study drug:	Angal S, topical spray [menthol], 0.5 mg + 2 mg/1 ml (Sandoz d.d., Slovenia)
Protocol version and date:	1.0 of September 29, 2016
Statistical Analysis Plan version and date:	1.0 of February 15, 2017

Document version history:

Version	**Reason for changes**
Version 1.0 (February 15, 2017)	Initial version

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1 Introduction

This trial has been designed and conducted to evaluate non-inferiority of the therapeutic efficacy and safety of the study drug Angal S, topical spray [menthol] containing 0.5 mg of lidocaine hydrochloride and 2 mg of chlorhexidine digluconate per ml (Sandoz d.d., Slovenia), when compared to ANTI-ANGIN® FORMULA, topical metered spray giving 0.12 mg of tetracaine hydrochloride and 0.24 mg of chlorhexidine bigluconate per dose (OOO Valeant, Russia) in the treatment of patients with uncomplicated acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat. The objective of this Phase III trial is to demonstrate the non-inferior therapeutic efficacy of the study drug as compared to the reference product.

This Statistical Analysis Plan was developed in accordance with the following documents:

- Guidelines for examination of medicinal products, Vol. 1. Federal State Budgetary Institution Scientific Center for Expert Evaluation of Medicinal Products under the Ministry of Health of the Russian Federation (eds. A.N. Mironov). Moscow: Grif and K, 2013.
- ICH harmonized tripartite guideline. Statistical principles for clinical trials (E9). Current Step 4 version dated 5 February 1998.
- GCP rules of the Eurasian Economic Union (a draft).

The objective of this Statistical Analysis Plan is more detailed, compared to Section 9 of the trial protocol, description of the main principles of the protocol-based statistical analysis, description of the primary and secondary endpoints analysis methods, as well as other data obtained during the trial.

This Plan stipulates for consistence of the scheduled and conducted statistical analysis to the trial protocol, including definition of the analysis data sets, transformations and calculations for the endpoints, observations quantity needed, etc. No changes in this Statistical Analysis Plan compared to the trial protocol are envisaged.

2. Trial endpoints

2.1 Primary endpoint

The primary outcome measure was the proportion of patients without sore throat after 3 days of therapy, as evaluated by the Investigator according to the Tonsillopharyngitis Severity Score (TSS), in both Angal S and ANTI-ANGIN® FORMULA arms.

TSS, a questionnaire (point scale) for healthcare professionals, is used in clinical practice as well as clinical trials to evaluate dynamic changes of symptoms severity of the infection-inflammatory process in the throat (Bereznoy VV, Riley DS, Wassmer G, Heger M. Efficacy of extract of Pelargonium sidoides in children with acute non-group A beta-hemolytic streptococcus tonsillopharyngitis: a randomized, double-blind, placebo-controlled trial). One of such clinical trials with TSS questionnaire was conducted in 2005 in Germany, ©CRO Applertee AG. A version of TSS ©CRO Applertee AG was adapted for this protocol.

TSS (Tonsillopharyngitis Severity Score) is a questionnaire for evaluation of the following symptoms severity: pharyngalgia, difficulty in swallowing, salivation, hyperemia of pharyngeal mucosa, and body temperature increase according to a 4-point scale:

0 = no symptom;

1 = insignificant symptom;

2 = moderate symptom;

3 = significant symptom.

The axillary body temperature increase is rated as follows:

0 points: <37.5 °C;

1 point: 37.5 to <38.5 °C;

2 points: 38.5 to <39.5 °C;

3 points: ≥39.5 °C.

TSS is filled in by the Investigator based on the patient complaints and physical examination data. The Investigator summarizes the points obtained for every symptom to obtain a total sum of TSS points. A total sum of TSS points will be evaluated at screening to define the inclusion criteria and evaluate for the baseline level; measure efficacy of the therapy conducted in the both arms at Visit 2 (Day 4); as well as evaluate the disease outcome at Visit 2 (Day 4) and/or Visit 3 (Day 5), if applicable.

2.2 Secondary endpoints

- The frequency of ≥50% total score reduction according to the TSS questionnaire completed by the Investigator as compared to the baseline in both Angal S and ANTI-ANGIN® FORMULA groups at Visit 2 (Day 4).
- Total score reduction according to the TSS questionnaire, as well as a reduction in the symptoms (sore throat, difficulty in swallowing, salivation, erythema, and fever) after a 3-day therapy, at Visit 2 (Day 4), as compared to the baseline total score.
- A period of time required for disappearance of the disease symptoms, determined according to the patient's diary (subjective patient's evaluation), but no more than 5 days during the trial—for patients who have achieved the corresponding outcome.
- A proportion (%) of patients who fully recovered by Day 4 in Group A and by Day 5 in Group B (the outcome of a disease according to the objective evaluation by the Investigator, the total score according to the TSS questionnaire ≤ 2).
- A change in the sore throat intensity by 100 mm VAS (visual analogue scale filled in by the patient) at the beginning, after 3 days of therapy, and at the end of treatment in both groups.

VAS (visual analogue scale) to evaluate pharyngalgia severity:

The patient will fill in this scale at every visit to the trial site (Visits 1, 2, 3, where applicable). Calibrated scales 100 mm in length with the relevant measuring instruments will be provided for the clinical trial.

The patients should evaluate their pain severity according to VAS at every visit (if possible, before administration of the painkillers (if those are required) or the study drug/comparator drug).

2.3 Evaluation of the study drug safety and tolerance

Safety of the trial therapy is evaluated based on the systemic parameters (systolic and diastolic blood pressure, breathing rate, heart rate, body temperature, ECG), laboratory tests results, frequency of adverse events (AEs) and serious adverse events (SAEs). AEs nature and incidence (allergic reactions, burning sensation, discomfort) at the administration site will be evaluated throughout the trial. Global evaluation of treatment tolerability will be made by the patient and the physician according to the following scale:

Scores	Evaluation
0	Poor

1	Satisfactory
2	Good
3	Excellent

Evaluation of the study drug tolerability by the patient and the physician (points/scores) should be specified in the eCRF at Visits 2 or 3 (where applicable).

3 Main provisions for analysis

3.1 Study drugs and therapy schedule

The patients were randomized in 1:1 ratio to the following groups:

Main group: Angal S, topical spray [menthol], 0.5 mg + 2 mg/1 ml (Sandoz d.d., Slovenia), 3 to 5 consecutive presses on the actuator button, 6 to 10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy).

Control group: ANTI-ANGIN® FORMULA, topical metered spray, 1–2 sprays at a time, up to 6 times a day, for 5 days or until full recovery (TSS ≤ 2) (whichever occurs first during 5 days of therapy).

3.2 Serious protocol deviations

A serious protocol deviation (Item 11.3 of the trial protocol) is a deviation, which may, according to the estimate by the Investigator or a person assigned by the Investigator, result into withdrawal of the subject from the trial or withdrawal of his data from the statistical part of the trial. The deviations not referred to as serious ones shall be considered minor protocol deviations.

For the purposes of this analysis, the serious protocol deviations were defined as follows:

Description	Example/Explanation	Efficacy or safety	Excluded from population:
Violation of the inclusion and non-inclusion criteria	Inclusion criterion No. 5: e.g., inclusion of the patient with initial total TSS < 5	Efficiency	PP
Violation of the informed consent receipt procedure	Absence of the Informed Consent Form	Safety and efficacy	All

	Informed Consent Form was signed after randomization/initiation of therapy	Safety and efficacy	None
Randomization and study drugs	Prescription of the drug non-consistent with the randomization arm	Efficiency	PP
	Low compliance: the patient missed more than 3 doses of the study drug	Efficiency	PP
Concomitant drugs	The patient used prohibited drugs during the trial (or had used the drugs prohibited by the inclusion/exclusion criteria before the trial initiation)	Efficacy and safety	PP

A final list of serious protocol deviations will be compiled before the statistical analysis start. Every protocol deviation should be evaluated for the patient's exclusion from the PP data set or statistical analysis by the trial Sponsor representative. The decisions adopted and lists of patients included into the relevant data sets must be documented before the analysis initiation.

3.3 Data sets for analysis

The intention-to-treat (ITT) population: All randomized subjects who have received at least one dose of the study drug/placebo and have completed at least one visit aimed at evaluation of the efficacy parameters (i.e., at least all the procedures of Visit 1).

According to the protocol (Section 9) and with reference to ICH E9 requirements, the ITT population will be considered to be a population for statistical analysis in the equivalence trials (including non-inferiority trials).

The per protocol (PP) population: All randomized subjects who have completed participation in the trial in accordance with the protocol (have completed the prescribed period of treatment and follow-up without significant deviations from the protocol).

A primary endpoint analysis will be conducted both for the ITT (main analysis) and PP populations (additional analysis).

Similarly, all efficacy endpoints will be analyzed both for the ITT and PP populations.

The safety population (safety): All randomized subjects who received at least one dose of the study drug/comparator drug and completed at least one

safety evaluation visit (i.e., at least Visit 1). As distinct from ITT population, the safety population will be analyzed depending on actually received treatment (not only prescribed) (in case of difference between the prescribed and received therapies).

The safety population will be used for all safety parameters including laboratory results, as well as for drug tolerability evaluation (see Section 2.3).

3.4 Subgroups

A subgroup analysis is not envisaged for this trial.

3.5 Data from various trial sites

This is a multicenter trial but data analysis for every particular trial site is not envisaged.

3.6 Missed data and outliers

At the database check, the expert in statistics authorized by the Sponsor and the data control and processing managers will analyze the trial results for questionable, missed and unanalyzable data, which will be the basis for the questions for investigators.

If possible, the investigators will eliminate the errors identified in CRFs and inform the Principal Investigator and authorized representatives of the Sponsor hereof. In case the identified data errors cannot be eliminated after the completion of the patients participation in the trial, the analysis of the resulting parameter sensitivity to questionable data will be conducted in the statistical analysis.

Information about the missed, questionable, and unanalyzable data will be summarized in the final clinical trial report.

The main analysis for the primary endpoint will be conducted without replacement for the missed, questionable, or unanalyzable data.

An additional analysis will be conducted with the data replacement (last observation carried forward); in this case, the last known TSS score will be carried to all subsequent control points.

All other data will be analyzed based on actually available information only, without data replacement.

Regarding abnormal test results, their clinical significance is evaluated by the Investigator during the trial with registration of AEs or adverse reactions, under control of the clinical trial specialists. Additional inquiries may be

forwarded to the trial sites (before the cut-off date) if clinical significance of the abnormal test results is hard to evaluate.

3.7 Interim analysis

An interim analysis may be conducted by the Sponsor's decision after receipt of efficacy data for Angal S and ANTI-ANGIN® FORMULA, spray, after 3 days of therapy, on Day 4, for at least 100 patients in every arm. The interim analysis includes demographic data, data of anamnesis and concomitant therapy, available data on efficacy and safety of Angal S and ANTI-ANGIN® FORMULA spray.

Safety will be evaluated for all the patients who received at least one dose of the study drug as at the interim analysis date. Based on the interim analysis results, the main and additional statistical parameters of efficacy and safety of the study drug, ZAO Sandoz shall be entitled to decide to discontinue the trial prematurely.

No significance level correction for the interim statistical analysis is envisaged.

3.8 Acceptable deadlines for visits and a scope of investigations

The data obtained at Visit 1 (Day 1) will be considered to be the initial data for the endpoint analysis.

3.8.1 Screening: Visit 1 (Therapy Day 1)

Visit 1 is scheduled for Day 1. At this visit, the doctor evaluates the patient's eligibility for the trial. If no non-inclusion criteria are met, the patient undergoes randomization, is given the study drug/comparator drug and a patient's diary, and is instructed on the patient's diary completion requirements.

Screening visit procedures:

- Signing of the Informed Consent Form;
- Demographic data (date of birth, sex, age);
- Measurement of weight and height;
- Anamnesis gathering;
- Records on the concomitant therapy;
- Evaluation of inclusion/non-inclusion criteria;
- Evaluation of the throat pain intensity according to VAS;
- Fill-in of TSS questionnaire by the Investigator;

- Physical examination (including oropharynx);
- Measurement of the main vital signs;
- Hematology;
- Biochemistry;
- Urine pregnancy test;
- 12-lead ECG;
- Evaluation of inclusion/non-inclusion criteria;
- Randomization;
- Training for administration and handling of the study drugs;
- Dispensing of the study drugs;
- Provision with the patient's diaries and training on the fill-in rules;
- Initiation of therapy with the study drugs;
- Evaluation of adverse events (including based on results of the throat and pharynx examination).

3.8.2 Efficacy evaluation visit (Visit 2, Day 4 since the therapy initiation)

Visit 2 is conducted on Day 4; the patient must visit the trial site in the fasted state and bring the filled-in diary and unused drug. If Group B patients (ANTI-ANGIN® FORMULA) did not meet recovery criteria (total TSS ≤ 2) at Visit 2 (Day 4), they will require continuation of the therapy, and some procedures for those patients will be transferred for the next day (Visit 3, Day 5), see below. The patients will keep their diaries and the unused drugs.

Visit 2 procedures for the both groups:

- Collection of complaints, actualization of anamnesis;
- Records on the concomitant therapy;
- Physical examination (including oropharynx);
- Measurement of the main vital signs;
- Evaluation of adverse events (including based on results of the throat and pharynx examination);
- Evaluation of exclusion criteria;
- Compliance evaluation (diary completion, administration of the study drugs).

Visit 2 procedures for patients from Group A (Angal S) and Group B (ANTI-ANGIN®FORMULA) who achieved recovery criteria (total TSS ≤ 2):

- Hematology;
- Biochemistry;
- 12-lead ECG;
- Global evaluation of treatment tolerability during the trial by the physician and the patient;
- Return of the unused study drug;
- Return of the patient's diary.

3.8.3 Trial completion visit for Group B patients (Visit 3, Day 5)

This visit is for Group B patients only (ANTI-ANGIN® FORMULA) who did not achieve the recovery criteria (total TSS ≤ 2) at Visit 2 (Day 4).

Visit 3 is conducted on Day 5; the patient must visit the trial site in the fasted state and bring the filled-in diary and unused drug.

Visit 3 procedures:

- Collection of complaints, actualization of anamnesis;
- Records on the concomitant therapy;
- Physical examination (including oropharynx);
- Measurement of the main vital signs;
- Evaluation of adverse events (including based on results of the throat and pharynx examination);
- Evaluation of exclusion criteria;
- Return of the unused study drug;
- Return of the patient's diary;
- Compliance evaluation (diary completion, administration of the study drugs).
- Hematology;
- Biochemistry;
- 12-lead ECG;
- Global evaluation of treatment tolerability during the trial by the physician and the patient.

3.8.4 Visit 4 (a follow-up, Day 6/7 from the therapy initiation)

A follow-up visit shall be conducted by phone to find out about the patient's state and any AEs. A visit 2 days after

the therapy completion visit (e.g., on Day 6 or 7, depending on the arm and therapy duration).

Follow-up visit procedures (by phone):

- Evaluation of adverse events (without the throat and pharynx examination). In case of adverse events, the patient might be invited to visit the trial site.

3.8.5 Unscheduled visits

The unscheduled visits will be conducted when necessary, e.g., in case of the index disease deterioration, AEs, or the study drug (Angal S or ANTI-ANGIN® FORMULA) intolerability.

Every unscheduled visit, irrespective of its cause, must include the procedures listed below with completion of the relevant eCRF pages (Unscheduled Visit):

- Physical examination (including topical examination);
- TSS evaluation;
- Measurement of the main vital signs (blood pressure, heart rate, breathing rate, body temperature);
- 12-lead ECG (if it has not been done for the last 12 hours);
- Evaluation of adverse events;
- Evaluation of the concomitant therapy.

Other diagnostic and treatment procedures may be conducted depending on clinical situation and upon the Investigator's decision.

Taking into account frequency of visits, unscheduled visits may be conducted on the same days as scheduled ones but in a different time (e.g., in case of worsening the patient may visit the center in afternoon). All procedures for the scheduled visits are identical for the both arms at every trial stage, except for the Group B patients who, if the recovery criteria (total TSS ≤ 2) are not met at Visit 2 (Day 4), should continue the trial therapy and visit the trial site for scheduled Visit 3 Day 5).

3.8.6 Visit of premature discontinuation of the trial

Visit 2 procedures will be applied for the visit of premature discontinuation.

3.9 Null and alternative trial hypotheses

Based on the trial objectives, the following hypotheses were drawn for testing:

Null hypothesis (H0): Difference in the primary endpoint achievement incidence while using Angal S, the study drug, and ANTI-ANGIN®FORMULA, the original drug, for treatment of acute infectious and inflammatory pharyngeal diseases will exceed 14.5% in favor of ANTI-ANGIN® FORMULA:

$$\mathbf{H_0: } p_1 - p_2 \leq -0.145$$

Alternative hypothesis (Ha): Difference in the primary endpoint achievement incidence while using Angal S, the study drug, and ANTI-ANGIN® FORMULA, the original drug, for treatment of acute infectious and inflammatory pharyngeal diseases will not exceed 14.5% in favor of ANTI-ANGIN® FORMULA:

$$\mathbf{H_A: } P_1 - P_2 > -0.145$$

Where p1 and p2 is the primary endpoint achievement incidence while using Angal S, the study drug, and ANTI-ANGIN® FORMULA, the original drug, respectively.

3.10 Significance level

All statistical analyses in this trial will be conducted at 95% significance level (a threshold p value for confirmation of statistical significance is below 0.05), except for the primary endpoint where a one-sided statistical criterion will be used with 95% significance level (a threshold p value is below 0.05). The two-sided statistical criteria will be used for all other parameters.

For the primary endpoint evaluation, 90% CI will be calculated for the proportions difference with further evaluation of its lower boundary limit.

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For non-inferiority confirmation, a two-sided 90% CI will be calculated for the proportion difference of the primary efficacy parameters (no pain after 3 days of therapy on Day 4 according to TSS) with further evaluation of its lower boundary limit.

A non-inferiority conclusion will be made relating to the primary parameter only which will confirm the claimed efficacy. Secondary variables (including secondary efficacy and safety parameters) will be used for the research interest. Correction for multiple comparisons is not envisaged due to the trial arms number.

Descriptive statistics will include data for all randomized patients. Descriptive statistics parameters to be calculated for the quantitative variables are listed below:

- Quantity of observations (n);
- Arithmetic mean (M);
- Standard deviation (SD);
- 95% confidence interval for the mean (95% CI);
- Minimal value (min.);
- Maximal value (max.);
- Median (Me);
- Interquartile range (IQR).

For the variables presented as qualitative and serial parameters, the absolute (n) and relative (%) incidences will be calculated for every category, as well as 95% CI (unless otherwise specified).

4.1.1 Descriptive statistics

Descriptive statistics for the initial data (obtained during Visit 1) for all randomized patients will be presented for the following variables:

- Age (a number of complete years as at Visit 1 date based on the date of birth);
- Sex, race;
- Social habits;
- Vital signs: initial systolic blood pressure, diastolic blood pressure, breathing rate, body temperature;
- Physical examination (presence/absence of deviations from the reference for organs and organ systems);
- Hematology, biochemistry;
- Electrocardiogram: presence/absence of deviations;
- Throat pain intensity according to VAS;
- TSS evaluation;
- Symptoms duration (calculated as a number of days as at Visit 1 date based on the first signs occurrence date);
- Time since the diagnostics to the therapy initiation (calculated as a number of days as at Visit 1 date based on clinical diagnostics date);
- Concomitant diseases: rate for the main organs and systems (MedDRA terms);
- Concomitant therapy: rate for the main drug groups;

Descriptive statistics for the data obtained by Visits 2 and 3 will be presented for the following variables:

- Vital signs: systolic blood pressure, diastolic blood pressure, breathing rate, body temperature;
- Physical examination (presence/absence of deviations from the reference for organs and organ systems);
- Throat pain intensity according to VAS;
- TSS evaluation;
- Evaluation of therapy efficacy;
- Hematology, biochemistry;
- 12-lead ECG;
- Global evaluation of treatment tolerability;
- Compliance evaluation;

All the AEs and SAEs registered during the trial will be classified according to MedDRA terms. A percentage of patients with the registered AEs with relevant codes (according to MedDRA terms and term groups) will be presented for every trial arm. In addition, AEs will be classified for severity and relationship with the study drug/comparator drug.

Descriptive statistics will be presented for all parameters for each group separately.

4.1.2 Primary endpoint

The primary endpoint of the trial (absence of the sore throat after 3 days of therapy on Day 4) will be presented as the difference between the proportions for each arm. The group comparison will be carried out using the Fisher's exact test (one-sided test, in connection with the null hypothesis of non-inferiority). For the proportion difference, the 90% confidence interval (CI) will be calculated according to the procedure described in Newcombe, Robert G. "Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods," Statistics in Medicine, 17, 873-890 (1998).

Thus, the non-inferiority will be confirmed if the limit of the two-sided 90% confidence interval for the difference in the proportions will be 14.5% or lower.

A primary endpoint analysis will be conducted both for the ITT (main analysis) and PP populations (additional analysis).

4.1.3 Secondary endpoints

The following statistical analysis methods are stipulated for the secondary efficacy endpoints:

- The frequency of ≥50% total score reduction by the TSS questionnaire completed by the Investigator relative to baseline in both Angal S and ANTI-ANGIN® FORMULA arms at Visit 2 (Day 4)—the response frequencies will be compared in each time point using the Fisher's exact test.
- Total score reduction by the TSS questionnaire, as well as reduction in symptoms (sore throat, difficulty in swallowing, salivation, erythema and fever) after 3-day therapy, at Visit 2 (Day 4), relative to baseline total score—the between-arm comparison will be carried out using the Mann–Whitney test due to non-symmetrical nature of the scores distribution in the TSS scale.
- A period of time required for the symptoms resolution defined by the patient's diary (subjective patient's evaluation), but not more than 5 days within the trial (for patients who achieved the relevant outcome)—the between-arm comparison will be carried out using t-test or the Mann–Whitney test depending on the distribution character. The survival will not be evaluated due to low duration of the trial.
- The proportion (%) of patients who fully recovered on Day 4 in Group A and on Day 5 in Group B (disease outcome according to the objective evaluation by the Investigator, the total score by the TSS questionnaire ≤ 2)—the between-arm comparison will be carried out using the Fisher's exact test.
- A change in the sore throat intensity by 100 mm VAS (visual analogue scale filled in by the patient) at the beginning, after 3 days of therapy, and at the end of treatment in both groups—the between-arm comparison will be carried out using the t-test.

A secondary endpoint analysis will be conducted both for the ITT (main analysis) and PP populations (additional analysis).

A multifactorial analysis of the secondary endpoints is not envisaged.

4.1.4 Safety and tolerability analysis

AEs incidence will be compared between the trial arms using Pearson's chi-squared test. In case of significant changes, a relative risk will be calculated (with 95% CI).

A tolerability level for every group will be calculated based on the AEs incidence and nature (in accordance with Section 2.3 of this Plan).

4.1.5 Analysis of laboratory and functional tests results

A between group comparison of the vital signs changes (systolic blood pressure, diastolic blood pressure, breathing rate, heart rate, body temperature) revealed at every visit (Visits 1, 2, 3) as well as laboratory results and ECG changes incidence obtained at Visit 1 and Visits 2–3 is envisaged. In addition, significance of the changes will be evaluated for all repeatedly measured parameters.

The following laboratory parameters will be reviewed:

- Hematology
  - Hemoglobin
  - RBC
  - ESR
  - WBC
  - Neutrophils
    - Juvenile
    - Stab
    - Segmented
  - Eosinophils
  - Basophils
  - Monocytes
  - Lymphocytes
- Biochemistry
  - Total protein
  - AST
  - ALT
  - Total bilirubin

ANOVA methods will be used to reveal a simultaneous influence of a group and time factors on the quantitative parameters.

The cross tables analysis will be used to reveal a correlation between the qualitative parameters (chi-squared test).

For the quantitative parameters, a comparison will be made by Student's t-test for the independent samples (in case of confirmation of hypothesis on normal variables distribution) or Mann–Whitney test (in case of rejection of hypothesis on normal

variables distribution); for the qualitative parameters—using Fisher's exact test.

To evaluate significance of the intragroup changes during the trial for repeatedly measured parameters, the paired Student's t-test (in case of confirmation of hypothesis on normal variables distribution) or paired Wilcoxon signed-rank test (in case of rejection of hypothesis on normal variables distribution) will be used; for the qualitative parameters McNemar's test will be used.

5 Presentation of statistical analysis results

5.1 Table templates

Table 1. Patient distribution

Patient distribution	Arm Number of patients (proportion, %)	Group Number of patients (proportion, %)
Included in the trial (screened)	n/N (%)	n/N (%)
Excluded at screening	n/N (%)	n/N (%)
Randomized	n/N (%)	n/N (%)
Discontinued prematurely	n/N (%)	n/N (%)
ITT population	n/N (%)	n/N (%)
PP population	n/N (%)	n/N (%)
Safety population	n/N (%)	n/N (%)

Table 2. Demographic and anthropometric patients' characteristics

Arm	Parameter	Age	Body weight	Height
	n			
	M			
	SD			
	95% CI			
	Min.			
	Max.			
	Me			
	IQR			
	n			
	M			
	SD			
	95% CI			
	Min.			
	Max.			
	Me			
	IQR			
p				

Table 3. Patients distribution by sex

Arm	Men	Women
	n/N (%)	n/N (%)
	n/N (%)	n/N (%)
p		

Table 4. Patients distribution by race

Race	Arm	Number of patients (proportion, %)	p
Caucasian		n/N (%)	
		n/N (%)	
Negroid		n/N (%)	
		n/N (%)	
Asian		n/N (%)	
		n/N (%)	
Unknown		n/N (%)	

		n/N (%)	
< Other >		n/N (%)	
		n/N (%)	

Table 5. Social habits: alcohol abuse

	Arm	Number of patients (proportion, %)	p
Non-user		n/N (%)	
		n/N (%)	
Former user		n/N (%)	
		n/N (%)	
Current user		n/N (%)	
		n/N (%)	

Table 6. Social habits: smoking

	Arm	Number of patients (proportion, %)	p
Non-smoker		n/N (%)	
		n/N (%)	
Former smoker		n/N (%)	
		n/N (%)	
Current smoker		n/N (%)	
		n/N (%)	

Table 7. The main vital signs (Visits 1, 2, 3)

Arm	Parameter	Systolic blood pressure	Diastolic blood pressure	Pulse rate	BR	Body temperature
	n					
	M					
	SD					
	95% CI					
	Min.					
	Max.					
	Me					
	IQR					
	n					
	M					
	SD					
	95% CI					
	Min.					
	Max.					
	Me					
	IQR					
	p					

Table 8. ECG results (Visits 1, 2, 3)

Arm	Parameter	ECG n/N (%)
	Reference	
	Deviation	
	Reference	
	Deviation	

Table 9.Hematology (Visits 1, 2, 3)

Arm	Parameter	Hemoglobin	RBC	ESR	WBC
	n				
	M				
	SD				
	95% CI				
	Min.				
	Max.				
	Me				
	IQR				
	n				
	M				
	SD				
	95% CI				
	Min.				
	Max.				
	Me				
	IQR				
	p				

Table 10. WBC differential (Visits 1, 2, 3)

Arm	Parameter	Neutrophils, total	Juvenile	Stab	Segmented	Eosinophils	Basophils	Monocytes	Lymphocytes
	n								
	M								
	SD								
	95% CI								
	Min.								
	Max.								
	Me								
	IQR								
	n								
	M								
	SD								
	95% CI								
	Min.								
	Max.								
	Me								
	IQR								
	p								

Table 11.Biochemistry (Visits 1, 2, 3)

Arm	Parameter	Total protein	ALT	AST	Total bilirubin
	n				
	M				
	SD				
	95% CI				
	Min.				
	Max.				
	Me				
	IQR				
	n				

	M				
	SD				
	95% CI				
	Min.				
	Max.				
	Me				
	IQR				
	p				

Table 12.A number of patients with normal and abnormal hematology parameters (Visits 1, 2, 3)

Arm	Parameter	Hemoglobin	RBC	ESR	WBC
	Reference				
	Deviation				
	Reference				
	Deviation				

Table 13.A number of patient with normal and abnormal WBC differential results (Visits 1, 2, 3)

Arm	Parameter	Neutrophils, total	Juvenile	Stab	Segmented	Eosinophils	Basophils	Monocytes	Lymphocytes
	Reference								
	Deviation								
	Reference								
	Deviation								

Table 14. A number of patient with normal and abnormal biochemistry parameters (Visits 1, 2, 3)

Arm	Parameter	Total protein	ALT	AST	Total bilirubin
	Reference				
	Deviation				
	Reference				
	Deviation				

Table 15. Concomitant diseases

Organ, system	Arm	Number of diseases (proportion, %)
		n/N (%)
		n/N (%)
		n/N (%)
		n/N (%)
		n/N (%)

Table 16. Concomitant therapy

Drug group	Arm	Number of prescriptions (proportion, %)
		n/N (%)

		n/N (%)
		n/N (%)
		n/N (%)
		n/N (%)

Table 17. Evaluation of throat pain severity according to VAS

Arm	Parameter	Visit 1	Visit 2	Visit 3
	n			
	M			
	SD			
	95% CI			
	Min.			
	Max.			
	Me			
	IQR			
	n			
	M			
	SD			
	95% CI			
	Min.			
	Max.			
	Me			
	IQR			
	p			

Table 18. TSS scores (Visits 1, 2, 3)

Arm	Amount of scores	Sore throat	Difficulty in swallowing	Salivation	Pharyngeal mucosa hyperemia	Fever
	0	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	1	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	2	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	3	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	0	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	1	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	2	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	3	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
	p	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)

Table 19. Frequency of the recovery criteria achievement (total TSS ≤ 2) by Visits 2, 3

Arm	Parameter	Visit 2	Visit 3
	Criterion is met		
	Criterion is not met		
	Criterion is met		
	Criterion is not met		

Table 20. Global evaluation of treatment tolerability (Visits 2, 3)

Arm	Parameter	Tolerability evaluation by the patient	Tolerability evaluation by the physician
	n		
	M		

	SD		
	95% CI		
	Min.		
	Max.		
	Me		
	IQR		
	n		
	M		
	SD		
	95% CI		
	Min.		
	Max.		
	Me		
	IQR		
	p		

Table 21. Registered adverse events occurred after initiation of the trial therapy

Description	Mild AEs		Moderate AEs		Severe AEs		Total		Total
	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious + non-serious
Organ system									
Organ system									

Table 22. Registered adverse events occurred after initiation of the reference therapy

Description	Mild AEs		Moderate AEs		Severe AEs		Total		Total
	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious + non-serious
Organ system									
Organ system									

Table 23. AEs frequency by the nosological groups

Nosological group	Arm	Arm	p
Nosological group 1	n/N (%)	n/N (%)	
Nosology 1	n/N (%)	n/N (%)	
Nosology 2	n/N (%)	n/N (%)	
Nosology 3	n/N (%)	n/N (%)	
Nosological group 1	n/N (%)	n/N (%)	
Nosology 1	n/N (%)	n/N (%)	
Nosology 2	n/N (%)	n/N (%)	

Nosology 3	n/N (%)	n/N (%)	

Table 24. Compliance evaluation

Arm	Parameter	Compliance
	n	
	M	
	SD	
	95% CI	
	Min.	
	Max.	
	Me	
	IQR	
	n	
	M	
	SD	
	95% CI	
	Min.	
	Max.	
	Me	
	IQR	
	p	

5.2 List of figures

Figure 1. TSS scores changes by visits and trial arms

For the parameters listed below: pharyngalgia, difficulty in swallowing, salivation, hyperemia of pharyngeal mucosa, and body temperature increase, as well as for total sum of scores

Figure 2. Difference in proportions of patients who achieved efficacy criteria in every arm, 90% CI

Figure 3. Incidence of TSS scores decrease for 50% or more in the trial arms

Figure 4. A period of time required for disease signs resolution according to the patient's diary and the trial arms

Figure 5. Proportions of fully recovered patients by the trial arms

In Group A by Day 4 and in Group B by Day 5

Figure 6. Dynamic changes of pharyngalgia severity according to VAS by visits and trial arms

Figure 7. Dynamic changes of vital parameters by visits and trial arms

For the vital signs listed below: systolic blood pressure, diastolic blood pressure, pulse rate, breathing rate, body temperature.

Figure 8. Dynamic changes of hematology parameters by visits and trial arms

For the parameters listed below: Hb, RBC, ESR, WBC, neutrophils (juvenile, stab, segmented), eosinophils, basophils, monocytes, lymphocytes.

Figure 9. Dynamic changes of biochemistry parameters by visits and trial arms

For the parameters listed below: total protein, AST, ALT, total bilirubin.

6 List of approvals

Full name	Position	Signature	Date
[redacted]	[redacted]	*/Signature/*	[redacted]
[redacted]	[redacted]		