CLINICAL TRIAL PROTOCOL

Trial title: A Prospective, Multicenter, Open, Randomized, Parallel Clinical Trial for Comparative Assessment of Efficacy and Safety of Angal, Lozenges [Menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), and ANTI-ANGIN® FORMULA, Lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia) in Treatment of Patients with Uncomplicated Acute Infectious and Inflammatory Diseases of the Pharynx Accompanied by a Sore Throat

Protocol No. TE_004_ANG_LOZ / NCT03095521

Protocol version: 1.0 of September 28, 2016

Study drug: Angal

International non-proprietary name: Lidocaine + Chlorhexidine

Dosage form and strength: lozenges, 1 mg + 5 mg

Trial phase: III

Trial Sponsor: ZAO Sandoz, Russia

Address: 72 Leningradsky Prospekt, bld. 3, 125315 Moscow, Russia

SPONSOR'S SIGNATURES

PROTOCOL APPROVAL:

Protocol title: A Prospective, Multicenter, Open, Randomized, Parallel Clinical Trial for Comparative Assessment of Efficacy and Safety of Angal, Lozenges [Menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), and ANTI-ANGIN® FORMULA, Lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia) in Treatment of Patients with Uncomplicated Acute Infectious and Inflammatory Diseases of the Pharynx Accompanied by a Sore Throat

Protocol No.: TE_004_ANG_LOZ

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Sponsor's representative:

ZAO Sandoz, Russia

Address: 72 Leningradsky Prospekt, bld. 3, 125315 Moscow, Russia

[redacted]

[redacted] (Full name of the authorized person)

[redacted] (Position)

[redacted]

/Signature/ [redacted]

Signature Date

Contract research organization (CRO) responsible for trial conduct

[redacted]

Principal Investigator's Signature

Hereby I promise to:

- Take over the responsibility for the proper conduct of the trial at this trial site;
- Conduct the trial in accordance with this protocol, any further amendments thereto, or all other documents describing the trial conduct, which may be provided by ZAO Sandoz;
- Introduce no amendments to the trial protocol without the Sponsor's consent and written approval of those amendments by the Ethics Council, except for the cases when such a delay may inflict harm to the patients' health, or administrative amendments (in accordance with all regulatory requirements);
- I am fully aware of the instructions for use of the study drugs described in this protocol and all other information provided by the Sponsor, including current version of the Investigator's Brochure;
- I am familiar with the Good Clinical Practice rules (ICH GCP) and undertake to comply with them and all the applicable regulatory requirements;

All the individuals assisting me during the trial are adequately informed on Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), the study drug, and their responsibilities during the trial as described in this protocol.

Principal Investigator:

Full name and position of the Principal Investigator	Site title	Address, phone
Signature: _____ Date: _____ ____, 201_		

List of abbreviations

BP	Blood Pressure
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
B.V.	Vennootschap met beperkte aansparkelijkheid, Limited Liability Company
ST	Sore Throat
VAS	Visual Analogue Scale
ULN	Upper Limit of Normal
HIV	Human Immunodeficiency Virus
WMA	World Medical Association
IUS	Intrauterine System
IUD	Intrauterine Device
VNOK	Cardiology Society of the Russian Federation
WHO	World Health Organization
GmbH	Gesellschaft mit beschränkter Haftung, Limited Liability Company
GOST	The Russian State Standard
d.d.	delniska druzba, Public Limited Liability Company
DBP	Diastolic Blood Pressure
CI	Confidence Interval
EU	European Union
PI	Prescribing Information
Full name	First Name, Patronymic, Last Name
eCRF	Electronic Case Record Form
CRO	Contract Research Organization
MoH	Ministry of Health
NI	Minimum Efficiency
AR	Adverse Reaction
IEC	Independent Ethics Committee
AE	Adverse Event
OOO	Limited Liability Company
PVC	Polyvinyl Chloride
PTFCE	Polychlorotrifluoroethylene
RMOAG	The Russian Medical Society on Arterial Hypertension
MA	Marketing Authorization
RF	Russian Federation
SBP	Systolic Blood Pressure
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operational Procedure
ESR	Erythrocyte Sedimentation Rate
FZ	Federal Law
Full name	First Name, Patronymic, Last Name

BU	Bread Unit
BR	Breathing Rate
HR	Heart Rate
ECG	Electrocardiography, electrocardiogram
CTM	Clinical Trial Manager
CYP	Cytochrome P450
EHRM	European Health Risk Monitoring
GCP	Good Clinical Practice
ICH	International Conference for Harmonization
ITT	Intention-To-Treat
LD50	Lethal Dose 50%
LPPV	Local Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Affairs
NYHA	New York Heart Association
PP	Per-Protocol
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSS	Tonsillopharyngitis Severity Score

Table of Contents

1. Protocol synopsis

Trial title	A Prospective, Multicenter, Open, Randomized, Parallel Clinical Trial for Comparative Assessment of Efficacy and Safety of Angal, Lozenges [Menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), and ANTI-ANGIN® FORMULA, Lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia) in Treatment of Patients with Uncomplicated Acute Infectious and Inflammatory Diseases of the Pharynx Accompanied by a Sore Throat
Trial code	TE_004_ANG_LOZ
Sponsor	**ZAO Sandoz**
Study drug	Angal, lozenges [menthol], containing 1 mg of lidocaine hydrochloride and 5 mg of chlorhexidine dihydrochloride [redacted]
Reference drug	ANTI-ANGIN® FORMULA, lozenges, containing 0.2 mg of tetracaine hydrochloride, 2 mg of chlorhexidine diacetate, and 50 mg of ascorbic acid [redacted]
Clinical trial phase	III
Trial population	Up to 280 patients are planned to be included (randomized) into the trial (140 patients in every treatment arm) with probable withdrawal of not more than 10% patients during the trial. A minimal number of patients required for the statistical analysis is 256 (128 patients in every treatment arm) provided that they completed the trial according to the protocol.
Scheduled trial duration	Not more than 7 days: Screening/randomization/initiation of trial therapy: Day 1. Therapy duration: up to 5 days depending on the trial arm. A follow-up visit (on the phone): 2 days after the last scheduled visit to the trial site. Total enrollment duration: 8 months.
The number of trial sites	up to 20

Trial objective	This trial has been designed to evaluate the non-inferior therapeutic efficacy and safety of the study drug Angal, lozenges [menthol] 1 mg + 5 mg (Sandoz d.d., Slovenia), comparing to ANTI-ANGIN® FORMULA, lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia), in treatment of patients with uncomplicated acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat.
Trial goals	**Primary goal:** • Evaluation of non-inferiority of the therapeutic efficacy of Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6–10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy), compared to ANTI-ANGIN® FORMULA, lozenges 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (whichever occurs first during 5 days of therapy) in the treatment of patients with uncomplicated acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat. **Secondary goals:** • Evaluation of safety of Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6–10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy), compared to ANTI-ANGIN® FORMULA, lozenges 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (whichever occurs first during 5 days of therapy) in the treatment of patients with uncomplicated acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat. • Evaluation of adverse events (AEs) in the trial arms. • The AEs rate comparison between the trial arms.

Trial methodology	**Trial design** A prospective, multicenter, open-label, randomized, parallel group clinical trial. **Trial periods**: I. Screening + Randomization + Therapy initiation: Visit 1 (Day 1) II. Therapy with Angal (up to 4 days) or ANTI-ANGIN® FORMULA (up to 5 days): Visit 2 (Day 4) for the both trial groups Visit 3 (Day 5) for Group B patients III. Follow-up: Visit 4 (Day 6/7) phone contact **Visit 1 (Day 1):** The patient's participation in the trial starts since signing of the Informed Consent Form. The following test results are used to decide on the patient's inclusion into the trial: • 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; • 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). After the screening tests completion, on the same day, the patients who meet all the inclusion criteria will be randomized into one of the two trial groups (arms): Angal or ANTI-ANGIN® FORMULA. Therapy group will be assigned by randomization (in 1:1 ratio). The patients will be given the relevant study drugs and the patient's diaries. The first use of the drug corresponding to the assigned therapy group on Day 1 after randomization will be considered to be the treatment initiation (for the both groups). The patients will be instructed on how to fill in the patient's diaries. **Group A, therapy with Angal**: 1 lozenge with a not less than 2-hour interval, up to 6–10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy). A single dose of Angal is 1 lozenge. The lozenges are intended for full dissolution in the oral cavity. One lozenge is slowly disintegrating in the mouth. **Group B, therapy with ANTI-ANGIN® FORMULA** 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (whichever occurs first during 5 days of therapy). One dose of ANTI-ANGIN® FORMULA is 1 lozenge. The lozenges are intended for full dissolution in the oral cavity. One lozenge is slowly disintegrating in the mouth. Visits during therapy with Angal or ANTI-ANGIN® FORMULA During Days 2 and 3 of the therapy, the patients (in the both groups) do not visit the trial site. In case of worsening, including signs of the secondary bacterial infection, the patients must inform the Investigator who may decide on early discontinuation of the study drug. In this case, an unscheduled visit to the trial site is required.

Visit 2 (Day 4):

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 Group A patients (Angal) 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;

Visit 3 (Day 5):

Evaluation of the disease outcome based on TSS questionnaire for the Group B patients who continued therapy after Visit 2 (Day 4).

- 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. Group B patients should complete the therapy on Day 5 (unless it had happened earlier). In case of worsening or preservation of the disease signs by the last therapy day, further treatment will be given in accordance with the current medical care standards established in this health care facility. **Visit 4 (Day 6/7) (follow-up):** 2 days after the last scheduled visit to the trial site. This visit means a phone contact with the patient. Aim of this contact is to gather safety information (AEs). **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 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; • In case of indications/conditions, any of the trial procedures may be additionally performed upon the decision of the Principal Investigator. 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).
The main efficacy and safety evaluation parameters	**Primary outcome measure** The primary outcome measure was the percentage of patients **without sore throat after 3 days of therapy on Day 4, as** evaluated by the Investigator according to the Tonsillopharyngitis Severity Score (TSS), in both Angal and ANTI-ANGIN® FORMULA arms. **Secondary outcome measures** The secondary outcome measures in the both therapy groups were: • The frequency of ≥50% total score reduction according to the TSS questionnaire completed by the Investigator as compared to the baseline in both Angal and ANTI-ANGIN® FORMULA groups at Visit 2 (Day 4). • Total score reduction according to the TSS questionnaire, as well as 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 disease symptoms relief, 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).

- 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 the therapy, and at the end of the therapy in both groups.

TSS questionnaire

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 used at screening

	to evaluate for a subject's eligibility and baseline evaluation; at Visit 2 (Day 4), to measure efficacy of the trial therapy in the both groups; to evaluate the disease outcomes on Visit 2 (Day 4) and/or Visit 3 (Day 5), where applicable. **Safety evaluation criteria:** The following parameters will be taken into account for the safety evaluation: • AEs and/or SAEs rates per trial arms; • Global tolerance evaluation during the trial by the Investigator and patient; • Vital signs (heart rate, blood pressure, body temperature, breathing rate); • ECG parameters; • Laboratory results. The AEs will be described according to the scheme given below: • ae description; • ae severity; • ae duration; • Relation to the study drug; • Outcome. All AEs will be coded according to MedDRA terms.
Inclusion criteria	The patients who meet all the inclusion criteria listed below will be included in the trial: 1. The Informed Consent Form voluntarily signed by the patient. 2. Men and women at the age of 18 to 45 years old, inclusively. 3. Diagnosis of acute, uncomplicated, inflammatory and infectious condition of the pharynx associated with the inflammation and pain in the throat. 4. Manifestation of the first signs of acute, uncomplicated, inflammatory and infectious condition of the throat (pharyngitis and/or tonsillitis) not more than 48 hours before the inclusion.

	5 A baseline total sum of TSS (Tonsillopharyngitis Severity Score) points ≥5. 6 Body temperature measured in the axillary cavity is less than 37.5 °C. 7 Women with childbearing potential should demonstrate a negative pregnancy test result at screening (except for the women after surgical sterilization or menopause for more than 2 years) and use the established contraception methods for at least 3 months before the initiation of the trial therapy and 1 month after completion of the trial. 8 Men should use adequate contraception during the trial, since signing of the Informed Consent Form and till the trial completion, and for 30 days after the trial completion. 9 Ability to understand the presented information on the clinical trial, readiness to comply with the protocol, ability to use the study drugs by oneself and evaluate the symptoms according to VAS (visual analogue scale) or other questionnaires according to the protocol.
Non-inclusion criteria	The patients who comply with at least one of the criteria listed below will not be included: 1. Prior tonsillectomy, tonsillotomy. 2. Chronic conditions of the nasopharynx or oropharynx, ulcerative oral disorders. 3. A history of hypersensitivity or allergic reactions to any components of the study drugs or local anesthetics. 4. Use of analgesics during less than 12 hours before the trial start and/or impossibility to discontinue the analgesics for the trial period. 5. Use of antibiotics during less than 48 hours before the trial start and/or planned use of antibiotics during the trial. 6. Use of topical drugs (aerosols, gargle solutions, fast-disintegrating tablets/lozenges/pastilles) in the pharynx during less than 12 hours before the trial start and/or impossibility to discontinue

	those topical drugs, except for the study drugs, for the trial period. 7. Use of the systemic, inhalation, or nasal glucocorticosteroids during 30 days before the trial start and/or planned use of the glucocorticosteroids (except for the topical skin drugs) during the trial. 8. Impossibility to discontinue other drugs which might influence the trial results, e.g. antiviral or prohibited concomitant drugs (see *Prohibited concomitant therapy* section), for the trial period. 9. Signs of a primary bacterial pharyngitis or secondary bacterial infection (including body temperature increase above 37.5 °C, purulent pharyngeal pellicles, significant intoxication, leukocytosis, neutrocytosis, WBC differential's shift to the left (increase in stab neutrophils, presence of younger neutrophils), ESR more than 30 mm/h). 10. Granular pharyngitis. 11. Signs of rhinitis, sinusitis, otitis, eustachitis, laryngitis, tracheitis, bronchitis (such conditions require therapy which might influence the trial results). 12. Phenylketonuria. 13. Deficit of saccharase or isomaltase (according to anamnesis data). 14. Glucose-galactose malabsorption (according to anamnesis data). 15. Fructose intolerance. 16. Diabetes mellitus. 17. Glucose-6-phosphate dehydrogenase deficiency (according to anamnesis data). 18. Hemochromatosis. 19. Anemia (Hb less than 120 g/l according to hematology test). 20. Hyperoxaluria. 21. Urolithiasis. 22. Myasthenia. 23. Severe, uncontrolled, cardiovascular condition which, in the Investigator's opinion, preclude the patient from participation in the trial, namely: a. Severe (IV acc. to Canadian Cardiovascular Society) or unstable angina;

	b. Decompensated chronic heart failure (NYHA stage IV); c. Myocardial infarction for the last 6 months; d uncontrolled arterial hypertension (BP more than 180/115 mm Hg). 24. Pregnant and/or breastfeeding women. 25. Participation in other clinical trials at the screening visit or for 30 days before the screening visit. 26. Surgical intervention for 30 days before the screening visit or planned surgical treatment during the trial (sooner than a follow-up visit is completed), including diagnostic procedures or hospital stay. 27. Known or suspected narcotic/alcohol abuse. 28. A suspected low compliance or incapability of the patient to perform the procedures and comply with restrictions according to the trial protocol (e.g., due to mental disorders). 29. Any cardiovascular, renal, hepatic, gastrointestinal, endocrine, or nervous disorders, or any other conditions/diseases which, in the Investigator's opinion, might inflict harm to the patient's health.
Exclusion criteria	The patient may withdraw or be excluded from the trial based on the grounds listed below: 1. Negative course of the disease with signs of the secondary bacterial infection (including body temperature increase above 37.5 °C). 2. The Ethics Committee, regulatory authorities, or Sponsor terminate the trial or participation of the specific trial site for any reason. 3. The Investigator's decision to withdraw the patient from the trial in the interests of the patient. 4. Withdrawal of the informed consent (unwillingness of the patient to continue his/her participation in the trial). 5. Serious deviation from the trial protocol. 6. Individual intolerance of the study drugs. 7. Clinically significant adverse event or serious adverse event. 8. Patient's non-compliance.

	9. False inclusion (e.g., the patient was included in breach of the inclusion/non-inclusion criteria). 10. The patient complies with the non-inclusion criteria during the trial. 11. The patient receives or requires an additional therapy which might influence the trial results or patient's safety (see *Prohibited concomitant therapy* section). 12. Other conditions or events which, in the Investigator's opinion, require the patient's exclusion from the trial.
Prohibited concomitant therapy	The drugs listed below are prohibited for use throughout the trial period: 1. Topical drugs (aerosols, sprays, inhalations, gargle solutions, fast-disintegrating tablets/lozenges/pastilles) in the pharynx or nose. 2. Systemic, inhalation, or nasal glucocorticosteroids. 3. Systemic or topical (intranasal or pharyngeal) antibacterial drugs. 4. Anti-viral drugs. 5. Immunomodulatory agents. 6. Painkillers or antipyretic agents. 7. Class I antiarrhythmics. 8. Cholinesterase inhibitors (including neostigmine, distigmine, pyridostigmine) and other drugs for myasthenia.
Statistical analysis	A statistical objective of the trial will be a prove of a non-inferior therapeutic efficacy and safety of the study drug Angal comparing to the drug ANTI-ANGIN® FORMULA in the treatment of acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat. **The primary outcome measure: no pain in the throat after 3 days of therapy, i.e., on Day 4.** Justification of a non-inferiority margin and a sample size is based on the results of a placebo-controlled trial of lozenges with chlorhexidine and lidocaine [[redacted] Kris De Ceulaer. A summary of a clinical trial proves that chlorhexidine/lidocaine lozenges are effective and safe. 11-8-2015]. This trial has demonstrated absence of a sore throat (a TSS subscale) 3 days after the therapy initiation, on Day 4, in 62.5% patients

in the trial arm and 36.9% patients in the placebo arm (see the Table below).

	Baseline visit		D4	
N	**Product N=106**	**Placebo N=103**	**Product N=106**	**Placebo N=103**
Sore throat				
Unknown	0	0	2 (N=104)	0
Absent	0 (0%)	0 (0%)	65 (62.5%)	38 (36.9%)
Mild	3 (2.8%)	3 (2.9%)	27 (26.0%)	45 (43.7%)
Moderate	77 (72.6%)	75 (72.8%)	11 (10.6%)	19 (18.4%)
Severe	26 (24.5%)	25 (24.3%)	1 (1.0%)	1 (1.0%)
p	1.0000		0.0016	

Therefore, the lower limit of CI 95% for difference in a sore throat rate 3 days after the drug use, with account for 140 participants (2 outcomes in the study drug group are unknown) and 103 patients, may be calculated as follows:

NCSS 8.0 Two Proportions Report

Dataset Untitled

Zero Adjustment Method: None
Note: Exact tests and c.i.'s were not run because total count > 50
(specified under 'Reports' tab).

Table Section

				N1	N2	M1	M2	N
A	**B**	**C**	**D**	**(A+C)**	**(B+D)**	**(A+B)**	**(C+D)**	**(N1+N2)**
65	39	38	65	**103**	**104**	**104**	**103**	**207**

Confidence Intervals of Difference (P1-P2)

Interval Method	**Estimated Value**	**Confidence Limit**	**Confidence Limit**
Chi-Square (Pearson)	0.2561	0.1456	0.3666

(The calculation results are presented in the language of the original source)

In view of the considered nosology and absence of significant factors requiring a conservative approach for determination of the non-inferiority margin, for this purpose we can use a two-sided CI 90%. In such a case, the lower limit for the rate difference (a two-sided CI 95%) will amount to 14.6%. Therefore, a margin of 14.5% is considered to be justified.

Based on the above, we may hypothetically expect a rate of positive response to a new

	therapy (absence of a sore throat as an efficacy measure) at least 63%. A statistical hypothesis tested: H0: p_1-$p_2 \leq -14.5\%$ compared to H1: p_1-$p_2 > -14.5\%$ If a null hypothesis is rejected, a conclusion will be made that efficacy of the study drug is not less than that of the comparator drug. A sample size is evaluated based on the following assumptions: - A rate of positive response to therapy (absence of a sore throat as an efficacy measure) in a comparator drug arm is 63%. - A rate of positive response to therapy (absence of a sore throat as an efficacy measure) in a study drug arm is 65% (chosen within the tested hypothesis and based on the sample size and expected positive response). - Power = 80% - A non-inferiority margin: 14.5 - Significance level: 97.5% - Randomization in 1:1 ratio (study drug : comparator drug). A number of patients required at 80% power and 2.5% one-sided significance level to prove the hypothesis of the study drug efficacy not more than 14.5% inferior to that of the comparator drug (determined by absence of a sore throat after 3 days of therapy) is 128 patients in every arm.
Interim analysis	An interim analysis may be conducted after receipt of efficacy data for Angal and ANTI-ANGIN® FORMULA, spray, after 3 days of therapy, on Day 4, for 100 patients in every arm. The interim analysis includes demographic data, data on the anamnesis and concomitant therapy, available data on efficacy and safety of Angal and ANTI-ANGIN® FORMULA drugs.
Blinding, randomization	This trial will be open, without blinding. The patients will be included by randomization in 1:1 ratio using envelopes at the trial site.

2. Justification of trial and a drug clinical trials program

Trial rationale

A sore throat (pain in the throat) is one of the most common complaints addressed to the therapists and general practitioners. Viral or bacterial infections are the most probable causes of sore throat. Oropharyngeal mycoses cause sore throat more rarely. Pharyngitis is commonly associated with hyperemia of the back pharyngeal wall, palatopharyngeal arches, and tonsils. Approximately 70% of pharyngitis cases are caused by viruses. The most relevant and significant viruses are rhinoviruses, adenovirus, influenza, and parainfluenza viruses, coronaviruses, and a respiratory syncytial virus. Viral pharyngitis is not accompanied by pellicles but associated with other catarrhal symptoms, in addition to sore throat, such as sneezing and nasal stuffiness (1). In addition to the smooth diet, in accordance with the current clinical recommendations ("General Medical Practice" National Guidelines, 2013, and National Guidelines for the Otorhinolaryngology, 2008), the therapy of an acute, viral, uncomplicated pharyngitis is based on topical symptomatic drugs to arrest the throat pain: gargling with sage or chamomile infusion, synthetic antiseptics (myramistin, octenisept, chlorhexidine), fast-disintegrating tablets or pastilles containing a combination of antiseptic and anesthetic (Anti-Angin Formula, Hexalyse, Strepsils). In view of a high rate of acute pharyngitis (5 to 8 times per year according to the WHO), a range of drugs arresting the main signs of the disease and accelerating the patient's return to his/her usual daily activities always needs to be developed (2; 3; 4).

Angal (a combination of lidocaine and chlorhexidine), lozenges, 1 mg of lidocaine hydrochloride + 5 mg of chlorhexidine dihydrochloride (a composition for 1 lozenge), is planned to be registered in the Russian Federation. Angal is used for topical application by dissolution in the mouth to treat the signs of oral and pharyngeal inflammation and infections, such as uncomplicated pharyngitis and other conditions. Angal has been already registered in the European Union and Kazakhstan, but there is no similar drug in the Russian Federation. Current chlorhexidine/lidocaine combinations are registered in Russia in larger strengths and for other indications. Therefore, Angal may not be deemed as a generic drug.

Due to absence of an identical drug by composition for the purposes of a registration clinical trial, a comparative clinical trial of Angal with a similar drug (topical anesthetic + topical antibiotic) registered in Russia will be conducted. Among the commercially available drugs in Russia, the most suitable drug is ANTI-ANGIN® FORMULA, a combination drug containing chlorhexidine and tetracaine. ANTI-ANGIN®

FORMULA also contains ascorbic acid, the 3rd component, but its activity is not associated with the planned efficacy endpoint.
This trial design is based on the results of previous clinical III phase trial of the chlorhexidine/lidocaine combination: Clinical Trial for Assessment of Safety and Efficacy of a Echinacea/Sage Spray Compared to a Chlorhexidine/Lidocaine Spray in the Treatment of Acute Sore Throats (clinicaltrials.gov NCT00707902), as well as placebo-controlled trial of pastilles with chlorhexidine and lidocaine [redacted] Kris De Ceulaer. A summary of a clinical trial proves that chlorhexidine/lidocaine lozenges are effective and safe. 11-8-2015].

Drug clinical trials program

According to a clinical development program of Angal, lozenges [menthol, strawberry, honey, lemon], 1 mg + 5 mg, Sandoz is planning to conduct a clinical trial in the Russian Federation: *Prospective, Multicenter, Open, Randomized, Parallel, Clinical Trial for Comparative Assessment of Efficacy and Safety of Angal, Lozenges [Menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), and ANTI-ANGIN® FORMULA, Lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia) in Treatment of Patients with Uncomplicated Acute Infectious and Inflammatory Diseases of the Pharynx Accompanied by a Sore Throat.*
According to Federal Law *On Circulation of Medicines* No. 61-FZ of April 12, 2010 (as amended), a clinical trial with participation of Russia is required to register a drug in the Russian Federation. Therefore, the objective of this clinical trial is to establish at least non-inferior efficacy and safety of **Angal, lozenges [menthol]**, the study drug, compared to **ANTI-ANGIN® FORMULA, lozenges,** registered in Russia, in treatment of adults with acute, uncomplicated, infectious and inflammatory diseases of the pharynx accompanied by a sore throat.
Based on the results of this clinical trial of **Angal, lozenges [menthol],** Sandoz is planning for the state registration of **Angal, lozenges [menthol, strawberry, honey, lemon], 1 mg + 5 mg, within the same registration dossier.** The full composition of the lozenges for every flavor is presented in the Investigator's Brochure.

2.1 Names and description of study products

2.1.1 Study drug

Angal, lozenges [menthol], 1 mg + 5 mg.

Qualitative and quantitative composition
One lozenge contains chlorhexidini dihydrochloridum 5 mg and lidocaini hydrochloridum 1 mg.

Excipients: levomenthol 5 mg, anhydrous citric acid 5.5 mg, magnesium stearate 25 mg, sorbitol 1,208.5 mg.

Dosage form

Lozenge. White to off-white, round, slightly mottled lozenge.

Pharmacotherapeutic group: drugs for throat diseases treatment, antiseptics.

ATC code: R02AA05

Pharmacodynamics

Lidocaine hydrochloride is an amide local peripheral anesthetic. It has a surface analgesic effect, and does not prevent nerve conduction at the administration site.

As a local anesthetic, lidocaine has the same mechanism of action as other drugs from this group; it blocks the generation and conduction of nerve impulses in sensory, motor, and vegetative nerves. It primarily affects the cell membranes where it blocks the ion channels and thereby reduces the permeability for the sodium ions. Due to the progressive propagation of the anesthetic effect in the nerve, the electric stimulation threshold is increased, impulse conduction is slowed down, and the propagation of the action potential is contracted. Finally, conductivity is interrupted completely. Local anesthetics generally block autonomous nerve fibers, small non-myelinated (sensation of pain) fibers and small myelinated (sensation of pain and temperature) fibers more quickly than large myelinated fibers (sensation of touch and pressure).

On the molecular level lidocaine specifically blocks sodium ion channels in a non-active state and thus prevents generation of the action potential. This mechanism prevents the conduction of stimuli when lidocaine is used locally in the vicinity of nerves.

The effect on peripheral nerves is especially important if lidocaine is used as a local anesthetic. The efficacy-toxicity ratio is favorable. It very rarely causes allergic reactions. Chlorhexidine is a bisbiguanide cationic antiseptic. It is effective against gram-positive (e.g. Micrococcus sp., Staphylococcus sp., Streptococcus sp., Bacillus sp., Clostridium sp., Corynebacterium sp.) and, to a lesser extent, against gram-negative bacteria, especially in the vegetative form (it is not effective against spores at normal temperature). It also has an antimycotic effect on dermatophytes and fungi. It quickly inactivates the infectiousness of certain lipophilic viruses (influenza virus, herpes virus, HIV).

The drug exerts bacteriostatic effects in low levels and bactericidal effects in high levels.

The chlorhexidine molecule has a strong positive charge, and therefore adsorbs to the negatively charged areas on the cell surface.

The adsorption is specific and takes place in special parts of the bacterial cell wall. This damages the bacterial cell membrane's integrity, increasing its permeability.
Chlorhexidine binds to the cytoplasmatic bacterial membrane. It is also adsorbed onto the negatively charged surfaces of the teeth, plaque, or the oral mucosa, thereby persisting in the oral cavity for a long time after the drug use.

Pharmacokinetics

Chlorhexidine

Absorption

In oral or topical application, absorption of chlorhexidine is insignificant. In topical application on intact skin, chlorhexidine is adsorbed on the outside layers of the skin, providing long-term antimicrobial effect. Pharmacokinetic research has shown that after rinsing the oral cavity, approximately 30% of the total used amount of chlorhexidine is retained, which is then slowly released into the saliva. Approximately 4% of chlorhexidine is swallowed by the patient.

Distribution

The binding of chlorhexidine to the plasma proteins after oral use is not extensive.
Metabolism and elimination
Chlorhexidine is not accumulated in the body. The extent of its metabolism is insignificant. 10% of the absorbed active substance is excreted in the urine and 90% in the feces.

Lidocaine

Absorption

Lidocaine absorption varies depending on the site and the method of administration. It is rapidly absorbed from the gastrointestinal tract, mucous membranes and through broken skin; however, before entering the systemic circulation it is mostly decomposed. The absorption from mucous membranes after topical application depends on the circulation and the total dose. After 30 minutes, less than 17% of the dose taken is present in the stomach and the intestines in the unchanged form, while less than 1.5% is present in other tissues.

The anesthetic action of lidocaine after topical administration emerges after two to five minutes and lasts for 30 to 45 minutes. The anesthetic effect is limited to the surface and does not extend to the submucosal structures.

Distribution

Lidocaine is well distributed into tissues (kidney, lung, liver, heart, adipose tissue).

Lidocaine crosses the blood-brain barrier and placenta and is excreted in human milk.

Metabolism and elimination

It is metabolized during the first pass through the liver. Lidocaine undergoes dealkylation in the liver. The first two metabolites are pharmacologically active. These two active metabolites exert toxic effects on the central nervous system in some patients.
Lidocaine is eliminated in the form of metabolites through the kidneys. Approximately 10% is eliminated unchanged. The biological half-life of lidocaine is 1.5 to 2 hours in adults. The biological elimination half-life of lidocaine metabolites is 2 to 10 hours. The biological half-life is increased in congestive heart failure, liver diseases, and myocardial infarction.

Pharmacological properties

Angal, lozenges, contains 2 active substances.
The first is chlorhexidine, a bisbiguanide antiseptic, with an antimicrobial effect on gram-positive and gram-negative bacteria, especially in the vegetative form (it is not effective against spores at normal temperature). It exerts an antimycotic effect on dermatophytes and fungi. It quickly inactivates the infectiousness of certain lipophilic viruses (influenza virus, herpes virus, HIV). The susceptibility of individual bacterial strains varies. The drug exerts bacteriostatic effects in low levels and bactericidal effects in high levels.
The second active substance of Angal, lozenges, is lidocaine, an amide local anesthetic. It exerts local anesthetic effect.

Therapeutic indications

Angal, lozenges, have a dual effect (antimicrobial and anesthetic), and are therefore used locally for:

- Treatment of infections of the oral mucosa (stomatitis, gingivitis) and the throat;
- Pain relief in inflammation of the oral mucosa;
- Relief of symptoms of an inflamed throat (painful swallowing, irritation).

Dosage and method of administration

Angal lozenges are intended for topical application in the oral cavity and the throat.
One should dissolve the lozenges in the mouth slowly, one lozenge at a time; the active substances are released slowly and gradually with a topical effect.
Adults: per os, 6 to 10 lozenges per day, till full dissolution in the mouth. The maximum single dose for adults is 5 mg of chlorhexidine dihydrochloride and 1 mg of lidocaine hydrochloride.
The maximum daily dose is 50 mg of chlorhexidine and 10 mg of lidocaine.

Duration of treatment

Angal should not be used continuously for more than three to four days or too often. If during this time period the symptoms worsen or the patient has bacterial infection accompanied by elevated body temperature, this infection needs to be additionally treated.
Patients with diabetes mellitus
Angal, lozenges, contain sorbitol and can be used by diabetic patients.

Contraindications

- Hypersensitivity to the active substances (chlorhexidine or lidocaine), amide-type local anesthetics or to any of the excipients.
- Children under 5 years of age.
- Children with a history of muscle spasms (including fever-induced spasms), as Angal contains levomenthol.

Special warnings and special precautions for use

Bacterial infections with fever must be treated separately. In such cases, Angal pastilles can be used additionally for alleviating throat pain.
Caution must be used when administering the drug to patients with congestive heart failure or hepatic failure and in concomitant use of lidocaine analogues (class I antiarrhythmic drugs),

as adverse effects of lidocaine may be amplified.

Angal pastilles should be used with caution in patients with a tendency towards hypersensitivity reactions.
For self-treatment, Angal pastilles should not be used continuously for more than three to four days or too often. The drug should only be used until the inflammation-related throat pain or irritation persists.
The drug should not be used in patients with rare hereditary fructose intolerance.

Interaction with other drugs and other forms of interaction

Lidocaine is a known inhibitor of the CYP1A2 liver enzyme, and to a lesser extent the 2D6 and 3A4 enzymes. However, when used as recommended, the interactions with these enzymes are clinically insignificant.
The patients must not use Angal pastilles concomitantly with cholinesterase inhibitors (e.g., neostigmine, distigmine, pyridostigmine) and other drugs used to treat miasthenia.
The patients must not use Angal pastilles concomitantly with other topical antiseptics. This does not apply to Angal spray, which contains chlorhexidine and lidocaine, just like the pastilles. Single dose of the spray may be replaced with a single dose of lozenges. When combining the spray and the pastilles, the patient must not exceed the maximum daily dose. A combined use of Angal spray and lozenges in children is contraindicated.
Chlorhexidine is incompatible with anionic surfactants (e.g., sodium lauryl sulphate) and certain other substances (e.g., alginates, tragacanth) which are often present in tooth paste. Therefore, at least 30 minutes should elapse between using tooth paste and Angal pastilles.

Use during pregnancy and breastfeeding

Pregnancy

The changes in pharmacokinetics and/or pharmacodynamics of lidocaine during pregnancy may cause toxic effects. There are no controlled trials to date using chlorhexidine in pregnant women.

Breastfeeding

Lidocaine metabolites are excreted into the mother's milk; however, no adverse effects in infants were recorded. It is not known if chlorhexidine is distributed into breast milk.
Nevertheless, Angal should not be used in pregnant women and breast-feeding mothers, unless the benefits for the mother outweigh the risks for the child.

Fertility

No data is available on the effects of chlorhexidine and lidocaine on fertility in humans.

Effects on the ability to drive or operate machines

Trials of drug effects on the ability to drive and use machines have not been conducted.

Adverse events

In short-term topical application in the mouth and throat at recommended doses, the drug was tolerated well.
Classification of undesirable effect by organ systems according to MedDRA classification and frequency by organ systems:

- 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).

Blood and the lymphatic system disorders

Not known: methemoglobinemia.
Immune system disorders

Common: allergic skin reactions.
Rare: severe allergic reactions including anaphylactic shock.
Not known: delayed hypersensitivity reactions (contact allergy, photosensitisation) or other local reactions on the skin or teeth.
Psychiatric disorders

Not known: anxiety, agitation, euphoria.
Nervous system disorders

Not known: sleepiness, dizziness, poor orientation, confusion (also including speech), vertigo, shivering, dizziness, psychosis, nervousness, paresthesia, numbness, convulsions, loss of consciousness, coma.
Eye disorders

Not known: visual disturbances, including blurred or double vision.
Ear and labyrinth disorders

Not known: tinnitus.
Respiratory, thoracic, and mediastinal disorders

Not known: dyspnea, respiratory distress syndrome, respiratory depression, respiratory arrest.

Gastrointestinal disorders

Common: nausea, vomiting, abdominal pain.
Not known: difficulty swallowing, mouth sores.
Skin and subcutaneous tissue disorders

Rare: contact dermatitis.
Not known: lichenoid reaction.
Musculoskeletal and connective tissue disorders

Not known: twitching or tremor of the muscles.
General disorders and administration site conditions

Not known: asthenia, transient taste disturbance or burning sensation on the tongue, sensation of cold or hot.
Long-term continuous use of chlorhexidine in the oral cavity may result in a transient brown discoloration of the teeth. The discoloration can be removed. When the drug was limited to the throat area, there were no reports on discoloration of the teeth.

Overdose

Although the drug contains only a small fraction of toxic doses of both active ingredients and is used locally in the mouth, it can be inadvertently or accidentally overdosed. This can occur especially in children. Chlorhexidine is only absorbed in minimum amounts from the digestive tract. Lidocaine is absorbed more quickly, and its bioavailability is 35%. Toxic effects of lidocaine occur at plasma concentrations higher than 6 mg/l.
When excessive doses are used (more than 20 pastilles daily), there may be difficulty with swallowing (decreased control of the swallowing reflex).
Systemic intoxication is the consequence of the effect on the central nervous system and the vascular system. The first effects of overdose are disorders of the central nervous system.

Symptoms which can occur during systemic intoxication include: disturbances of the central nervous system: headache, hallucinations, vertigo, drowsiness, agitation, tinnitus, paresthesia, dysarthria, hearing disorders, perioral numbness, metabolic acidosis, nystagmus, muscular tremor, psychoses, convulsions, respiratory arrest, epileptic coma, reduced consciousness; cardiovascular disorders: acute cardiovascular insufficiency, severe bradycardia, heart rhythm disorders (sinus arrest, tachyarrhythmias), cardiac arrest.
In addition to the signs already mentioned, individual cases of chlorhexidine overdose are known. The symptoms listed below were observed: edema of the throat, necrotic injuries of the esophagus, increased serum aminotransferase concentrations (thirty times larger than the normal values), vomiting, stomach and duodenum erosion including active atrophic gastritis, euphoria, blurred vision and a total loss of taste (lasting for 8 hours).
Considering the data on acute, subacute, and chronic toxicity of both active ingredients, the risk of systemic effects of lidocaine, when used correctly is very small and predominantly associated with major misuse of Prescribing Information, as the doses of both active ingredients in the pastilles are very small.

Measures to be taken in case of systemic intoxication

If signs of intoxication appear, the drug must be discontinued immediately. Induce vomiting and perform gastric lavage. Use anionic agents. In severe cases, the patient must be hospitalized to prevent the collapse of breathing and circulation, as well as to prevent dehydration. Diazepam is the drug of choice for alleviating convulsions.

Preclinical safety data

Published non-clinical data suggests that chlorhexidine and lidocaine are well tolerated and show low toxicity.

Chlorhexidine

Chlorhexidine is virtually not absorbed when administered topically. In the urine of laboratory animals, only insignificant amounts of chlorhexidine were detected. The LD_{50} of chlorhexidine varies between species and ranges from 21 mg/kg (rats, intravenous) to 5,000 mg/kg (rats, oral). Sub-chronic toxicity trials showed minimal skin irritation (erythema, edema, peeling and/or cracking) in the smallest tested doses. No reproductive or developmental toxicity was shown at all the tested levels. No mutagenic effects were observed in *in vivo* mutagenesis trials evaluating chlorhexidine gluconate.
Long-term toxicity trials in rats showed no carcinogenic effects of chlorhexidine.

Lidocaine

LD50 of lidocaine varies between species and ranges from 19.5 mg/kg (mice, intravenous) to 317 mg/kg (rats, oral).
Lidocaine is neurotoxic due to its direct effect on sensory neurons and its induction of increased intracellular calcium ion concentration. Lidocaine is less cardiotoxic than bupivacaine. The neurotoxic effects that were noted after intrathecal infusion were dose-dependent.
No significant effects were observed in offspring of Sprague Dawley rats administered lidocaine.
Mutagenicity trials using the Ames test with lidocaine and its metabolites showed no mutagenic potential. In trials of chronic exposure to high doses of the metabolite lidocaine 2,6-xylidine, on rats with transplacentar exposure and those that received it in food after birth, this highly sensitive testing system detected the appearance of malignant and benign neoplasms, especially in the oral cavity.

Pharmaceutical parameters

Incompatibilities

Not applicable

Shelf life

3 years

Special storage conditions

Store at temperatures below 25 °C.
Store in original packaging; protect against moisture.
Special precaution for disposal and other handling

No special requirements.

Presentation:
10 or 12 lozenges (pastilles) in aluminum and PVC/PCTFE foil blister; 2 blisters in a carton pack.

12 lozenges (pastilles) in aluminum and PVC/PCTFE foil blister; 3 blisters in a carton pack.

2.1.2 Reference drug

ANTI-ANGIN® FORMULA, lozenges, 0.2 mg + 2 mg + 50 mg.
ATC code: R02AA20
Pharmacological groups

- Local anesthetics in combinations
- Antiseptics and disinfectants in combinations

Composition and presentation

Lozenges	1 lozenge
chlorhexidine diacetate	2 mg
tetracaine hydrochloride	0.20 mg
ascorbic acid	50 mg
Excipients: dextrose syrup 945.00 mg, saccharose 1,435.00 mg, natural oil flavoring 4.00 mg, mint flavoring 0.30 mg, red carmine colorant E120 0.10 mg, purified water 63.40 mg.	

Pharmaceutical form

Lozenges. 2, 4, 6, 8, 10, 12 lozenges in AL-PVC blister; 1, 2, 3, 4, 5, 10, 15 blisters in a carton pack.

Description of dosage form

Lozenges: flat, round, with beveled edges and rough surface, of pink to pinkish-red color, with a specific odor. Color non-uniformity, presence of air bubbles in a high-boiled sugar mass, and insignificant edge irregularity are allowed.

Pharmacological properties

Pharmacological effects: antiseptic and local anesthetic.

Pharmacodynamics

Chlorhexidine exerts the bactericidal and bacteriostatic effects.

It has a wide spectrum of antibacterial activity against gram-positive and gram-negative bacteria as well as *Candida albicans.* Chlorhexidine is especially effective against *Streptococcus mutans, Streptococcus salivarius, Escherichia coli,* and anaerobic bacteria. It is less effective against *Streptococcus spp., Proteus spp., Pseudomonas spp., Klebsiella spp., Veillonella spp.*
Tetracaine acts as a local anesthetic. An anesthetic effect develops 1–2 minutes after the drug use.
Ascorbic acid participates in collagen synthesis, tissue regeneration, and regulation of the oxidation-reduction processes, enhances the

immune reactions. Due to reduction in the capillary permeability, it contributes to decrease of inflammation and edemas of the mucous membranes of the mouth and pharynx.

Indications

Prevention and treatment of infectious and inflammatory oral and pharyngeal conditions (stomatitis, gingivitis, tonsillitis, pharyngitis, periodontosis, initial stage of paratonsillar abscess, condition after tonsillectomy or tooth extraction).

Contraindications

Hypersensitivity to the components of the drug, pediatric age below 5 years old, I pregnancy trimester, sucrase-isomaltase deficiency, fructose intolerance, glucose-galactose malabsorption, hypersensitivity to other topical anesthetics of the esters group or paraaminobenzoic acid or its derivatives.

Special precautions for use:

In II and III trimesters of pregnancy on doctor's prescription, during lactation, diabetes mellitus, glucose-6-phosphate dehydrogenase deficiency, hemochromatosis, sideroblastosis anemia, thalassanemia, hyperoxaluria, oxalosis, and urolithiasis.

Posology and method of administration

Topically, keep in the mouth till full dissolution.
Adults: 1 lozenge at a time every 2 hours but not more than 6 lozenges per day.

Side effects

Allergic reactions (in patients with hypersensitivity to the components of the drug).
Extension of the recommended duration of therapy may cause a temporal taste disturbance or tooth enamel deterioration (coloration, deposition of a tooth plaque).

Overdose

Symptoms: dizziness, general fatigue, cyanosis, agitation, anxiety, muscular tremor, respiratory disturbance, nausea, vomiting.
Treatment: gastric lavage, bulk cathartics; symptomatic treatment.

Interactions

Chlorhexidine is incompatible with anionic detergents (saponins, sodium lauryl sulfate, sodium carboxymethylcellulose). Concomitant use with iodine is not recommended. Ethanol enhances the drug effects.
Tetracaine reduces antibacterial activity of sulfanilamide agents. Vasoconstrictors prolong the activity and diminish toxicity of tetracaine. Ascorbic acid increases the blood levels of benzylpenicillin and tetracyclines. Ascorbic acid increases absorption of the ferric drugs in the intestine. It reduces efficacy of heparin and indirect anticoagulants. It increases the risk of crystalluria during therapy with the short-acting salicylates and sulfanilamides, reduces the plasma levels of oral contraceptives.

Special considerations

It is not recommended to use the drug concomitantly with iod-containing drugs for treatment of oral cavity and throat (Lugol's solution, povidone iodine). Ascorbic acid contained in the drug might influence some laboratory results which should become known during the tests.
Diabetic patients should note that each pastille contains 1.4 g of sucrose which corresponds to 0.12 bread units.
According to pharmacological properties, the product has no effect on the ability to perform the activities requiring increased concentration of attention and
prompt psychomotor reactions.
Long-term administration (more than 5 days) of the drug is undesirable due to possible damage to normal microbial flora of oral cavity and throat. Do not use the drug immediately prior to or during the meal. Do not brush your teeth after the drug use because the surface active agents contained in the toothpaste may inactivate chlorhexidine.
The drug may influence the doping test results.

Manufacturer

[redacted]

Storage conditions

At temperature below 25 °C.

Keep out of reach of children.

Shelf life

3 years. The drug should not be used after the expiry date.

2.2 Summary of preclinical and clinical results significant for this trial

Angal, a drug proposed for the state registration, contains two components; therefore, this section presents a summary of preclinical and clinical aspects of efficacy and safety of those components.

2.2.1 Preclinical results summary

2.2.1.1 Chlorhexidine (chlorhexidine dihydrochloride)

Chlorhexidine is a commonly used disinfectant and topical antiseptic agent. In vitro tests confirmed the value of chlorhexidine in the treatment of upper respiratory tract infections such as pharyngitis. It exerts bactericidal effects against the pathogenic bacteria in the upper respiratory tract infections. Chlorhexidine also shows some antiviral activity in relation to influenza A virus (H1N1).
Chlorhexidine is virtually not absorbed when administered topically. Small amounts are detected in the urine of laboratory animals. LD50 varies from 21 mg/kg (rats, i.v.) to 5,000 mg/kg (rats, oral). Subchronic toxicity trials showed minimal dermal irritation (erythema, edema, desquamation and/or fissuring) at the lowest dose tested.
Tests at all doses showed no malformations or developmental toxicity. Mutagenic effects were not observed in two mammalian in vivo mutagenesis trials evaluating chlorhexidine gluconate. Long-term toxicity trials in rats showed no carcinogenic effects of chlorhexidine (5; 6; 7; 8; 9; 10).

2.2.1.2 Lidocaine (lidocaine hydrochloride)

Lidocaine hydrochloride is a peripheral local anesthetic of the amide type. Lidocaine administered i.v. is used as an antiarrhythmic drug. Lidocaine, like other local anesthetics, blocks conduction of nerve endings impulses in a reversible way by interfering with processes fundamental to generation of nerve action potential, namely, large transient increase in permeability of membrane to sodium ions that is produced by slight depolarization of membrane.
From observations in rabbits administered lidocaine HCl i.v. and portally, a first pass hepatic elimination of approximately 30% could be calculated. The fraction of rectal venous drainage bypassing the portal circulation and thus hepatic metabolism is about 40%. In the rabbit, the hepatic first pass effect for lidocaine can be avoided by administering the compound via the rectum.

Intrinsic clearance of lidocaine was consistently reduced in the dog after repeated administration. LD50 varies from 19.5 mg/kg (mouse, i.v.) to 317 mg/kg (rat, oral). Lidocaine showed neurotoxicity to sensory neurons, resulting from a direct action on sensory neurons, and that a lidocaine-induced increase in intracellular Ca2+ is a mechanism of lidocaine-induced neuronal toxicity. Lidocaine is less cardiotoxic than bupivacaine. Observed neurotoxic effects after intrathecal infusion were dose-dependent. No significant effects were observed in offspring of Sprague Dawley rats administered lidocaine. Lidocaine did not show any mutagenicity. Lidocaine effectively inhibited the invasive ability of human cancer cells at concentrations used in surgical operations (11; 12; 13; 14).
For these reasons, the lozenges containing chlorhexidine hydrochloride (5 mg) / lidocaine hydrochloride (1 mg) are considered to be fully satisfactory for introduction to the market in terms of safety and efficacy. The information presented confirms the suitability of the product when used as recommended.

2.2.2 Clinical results summary

The results of a randomized, double-blind, placebo-controlled, phase III trial with a lemon-flavored lozenge formulation (Medica®) containing a combination of 5 mg chlorhexidine dihydrochloride with 1 mg lidocaine hydrochloride demonstrated higher efficacy than placebo regarding several measured parameters, which exhibited significant improvement from the stationary phase (sore throat at 120 min) through to the follow-up visit at Day 4 (sore throat and erythema). This combination was thus shown to provide symptomatic relief of sore throat as well as reducing signs of inflammation such as erythema. The combination lozenge was very well tolerated. In a double blind, placebo-controlled trial conducted by Schapowal et al., the use of a spray containing chlorhexidine 1% and lidocaine 2% demonstrated a 60% response on Day 3 of the therapy associated with a very good tolerability in patients with an acute tonsillopharyngitis (15).

The use of topical lidocaine forms (pastilles and spray) at much bigger strength than that of Angal was not associated with any toxic effects while a significant clinical effect was shown (16).
Although the overall volume of clinical evidence in support of the proposed indication is very limited and the available data set has not resulted from a systematic investigation of the properties of the product, this type of preparations has been used widely for several decades. The use of the drug at recommended doses for the approved indications is safe; the drug is registered in the EU; no SAEs were reported, while AEs and precautions for use in special

populations are well known and described in Section 2.1.1. Therefore, the repeated toxicological, pharmacological, or clinical trials for determination of the main features of the active substances are not justified, while a benefit/risk ratio is favorable to recommend conduction of a clinical trial of Angal in patients with acute viral pharyngitis.

2.3 Brief description of known and potential risks for the trial subjects (if any)

Preclinical and clinical trials of the study drugs components showed a favorable safety profile and good tolerability of Angal and ANTI-ANGIN® FORMULA. A list of known side effects of those drugs is presented in Section 2.2.1.

Venous blood will be collected during the trial, approximately 12 ml (1 tablespoonful) on Day 0 and Day 4, i.e., the total amount of blood taken for analysis will not exceed 30 ml for 5 days. Those volume and rate of a blood loss are clinically insignificant for an adult. Venipuncture may potentially cause a bruise or hematoma, as well as phlebitis or thrombophlebitis at the injection site. The trial site personnel will make every possible effort to minimize the risks for the patients associated with the trial therapy and procedures. In case of AEs or other health issues, the patient will be provided with the appropriate medical care.

The benefit from the trial is associated with the laboratory and instrumental investigations, therapy under supervision of a highly qualified doctors with the study drugs free of charge for the trial participants.

2.4 Description and rationale for the route of administration, dosages, dosing regimens, and duration of treatment

The study drugs will be prescribed according to relevant Prescribing Information: a Prescribing Information draft for Angal and a current Prescribing Information for ANTI-ANGIN® FORMULA registered in Russia.

Angal will be used in the following way: 1 lozenge with a not less than 2-hour interval, till full dissolution in the mouth, up to 6–10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy). ANTI-ANGIN® FORMULA will be used in the following way: 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (total TSS $\leq$ 2) (whichever occurs first during 5 days of therapy).

2.5 Legal basis

This is a protocol of clinical trial planned to be conducted in accordance with principles of the Declaration of Helsinki, World Medical Association (adopted at the 18th Assembly of the World Medical Association in Helsinki in June 1964, the latest revision adopted by the 64th Assembly in Fortaleza in October 2013), the triangular agreement on Good Clinical Practice (ICH GCP), and applicable laws of the Russian Federation:

- Federal Law *On Circulation of Medicines* No. 61-FZ of April 12, 2010 (current version No. 350-FZ of July 3, 2016).
- Federal Law *On Personal Data* No. 152-FZ of July 27, 2006 (current version of July 21, 2014 as amended as of September 1, 2015).
- The National RF Standard GOST R52379-2005, *Good Clinical Practice*.
- Government Decree of the Russian Federation No. 714 of September 13, 2010 (the last version of October 15, 2014), *Rules for compulsory insurance of the life and health of a patient involved in clinical trials of a drug*.
- Order of the Ministry of Health of the Russian Federation *On Approval of the Provision on the Ethics Council* No. 986n of November 29, 2012.
- Order of the Ministry of Health of the Russian Federation *On Approval of the Good Clinical Practice Rules* No. 200n of April 1, 2016.

2.6 Description of the trial population

Men and women at the age of 18 to 45 years old, inclusively, with acute, uncomplicated, inflammatory and infectious conditions of the pharynx associated with a sore throat, with manifestation of the first signs not more than 48 hours before the inclusion, with a total TSS ≥ 5, who signed the Informed Consent Form and comply with the inclusion criteria (see Section 5.1) and none of the non-inclusion criteria (see Section 5.2).

2.7 References

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3 Trial objectives and goals

3.1 Trial objective

This trial has been designed to evaluate the non-inferior therapeutic efficacy and safety of the study drug Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), comparing to ANTI-ANGIN® FORMULA, lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia), in treatment of patients with uncomplicated acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat.

3.2 Trial goals

Primary goal:

- Assessment of the non-inferior therapeutic efficacy of Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6–10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy), compared to ANTI-ANGIN® FORMULA, lozenges 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (whichever occurs first during 5 days of therapy) in the treatment of patients with uncomplicated acute infectious and inflammatory diseases of the pharynx accompanied by a sore throat.

Secondary goals:

- Assessment of safety of Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6–10 times per day, for 4 days or until full recovery (whichever occurs first during 4 days of therapy), compared to ANTI-ANGIN® FORMULA, lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia)—administration of 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (whichever occurs first during 5 days of therapy) in the treatment of patients with uncomplicated acute Infectious and inflammatory diseases of the pharynx accompanied by a sore throat.
- Evaluation of adverse events (AEs) in the trial arms.
- The AEs rate comparison between the trial arms.

4 Trial design

4.1 General and additional tested parameters

4.1.1 Efficacy parameters

4.1.1.1. The main efficacy endpoint

The primary outcome measure was the percentage of patients without sore throat after 3 days of therapy on Day 4, as evaluated by the Investigator according to the Tonsillopharyngitis Severity Score (TSS), in both Angal and ANTI-ANGIN® FORMULA arms.

4.1.1.2 Additional efficacy endpoints

The secondary outcome measures in the both therapy groups to compare the therapeutic efficacy of the study drug and comparator drug were:

- The frequency of ≥50% total score reduction according to the TSS questionnaire completed by the Investigator as compared to the baseline in both Angal 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 disease symptoms relief, 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.

4.1.2. Safety parameters

The following parameters will be taken into account for the safety evaluation:

- AEs and/or SAEs rates per trial arms;
- Global tolerance evaluation during the trial by the Investigator and patient;
- Vital signs (heart rate, blood pressure, body temperature, breathing rate);
- ECG parameters;
- Laboratory results.

The AEs will be described according to the scheme given below:

- ae description;
- ae severity;
- ae duration;
- Relation to the study drug;
- Outcome.

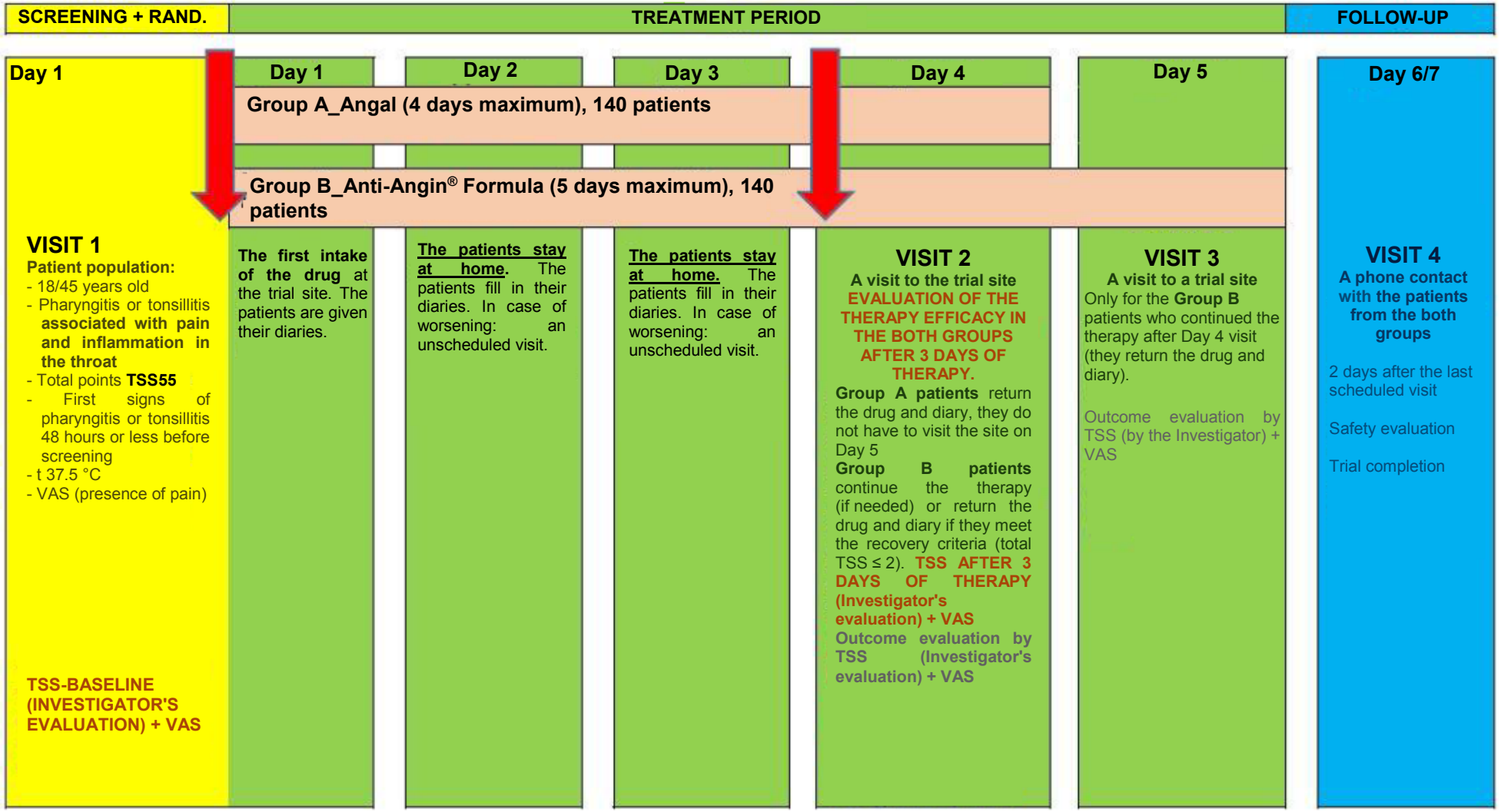
All AEs will be coded according to MedDRA terms.

4.2 Description of the trial design

4.2.1 Trial type

Prospective, multicenter, open, randomized, comparative, clinical trial in 2 parallel groups.

4.2.2 Trial design flowchart



4.2.3 Trial procedures

4.2.3.1 Trial procedures in a table form

Table 1. Visit schedule

Trial period	Screening/Randomization/Therapy initiation	Treatment		Further follow-up[1]	Unscheduled visits
Visits	Visit 1	Visit 2[2]	**Visit 3[3]**	Visit 4	
Day after initiation of therapy	Day 1	Day 4	**Day 5**	Day 6/7	
Trial procedures					
Signing of the Informed Consent Form	•				
Demographic data (date of birth, sex, age)	•				
Measurement of weight and height	•				
Medical history	•				
Collection of complaints, actualization of anamnesis	•	•	•		•
Records on the concomitant therapy	•	•	•		•
Evaluation of the throat pain intensity according to VAS by a patient	•	•	•		
Fill-in of TSS questionnaire[4]	•	•	•		•
Physical examination (including topical examination)	•	•	•		•
Measurement of vital signs[5]	•	• *	•		•
Hematology[6]	•	• *	•		
Biochemistry[7]	•	• *	•		
Urine pregnancy test[8]	•				
12-lead ECG	•	• *	•		
Evaluation of inclusion/non-inclusion criteria	•				

[1] A follow up visit will be held in the form of a phone contact with the patient to reveal the possible AEs.
[2] In case of premature discontinuation, the follow-up procedures are the same as those at Visit 2.
[3] **Only for the Group B patients who did not meet the recovery criteria (total TSS ≤ 2) at Visit 2 (Day 4) and continued the therapy.**
[4] Fill-in of TSS questionnaire by the Investigator (scores for every question should be summarized to obtain a total TSS score).
[5] Systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), breathing rate (per minute), pulse rate (beats per minute), axillary body temperature (°C).
[6] Hb, RBC, WBC with differential, ESR—at the trial site laboratory.
[7] Total protein, AST, ALT, total bilirubin.
[8] For women with the preserved childbearing potential only.

Trial period	Screening/randomization/therapy initiation	Treatment		Further follow-up[1]	Unscheduled visits
Visits	Visit 1	Visit 2[2]	**Visit 3[3]**	Visit 4	
Day after initiation of therapy	Day 1	Day 4	**Day 5**	Day 6/7	
Trial procedures					
Randomization	•				
Dispensing of the study drugs	•				
Dispensing of the patient's diaries	•				
Return of the unused study drugs		• *	•		
Return of the patient's diaries		• *	•		
Evaluation of adverse events (including based on results of the throat and pharynx examination during the trial site visits)	•	•	•	•	•
Evaluation of exclusion criteria		•	•		•
Global evaluation of therapy tolerability by the patient and the physician		• *	•		•
Compliance evaluation (diary completion, administration of the study drugs)		•	•		•

Notes:

* Only for Group A patients and those Group B patients who achieved the recovery criteria (total TSS score ≤2).

4.2.3.2 Description of the trial procedures

4.2.3.2.1 Collection of medical history, demographic and anthropometric data

Medical history includes the previous diseases, concomitant chronic conditions, hereditary issues, social habits (smoking, alcohol or drug abuse), allergological anamnesis, previous surgeries or traumas, occupational history, permanent or periodic drug therapy. Regarding the present condition: date and time of the first signs manifestation, diagnostic and treatment procedures by the screening, their efficacy. A contraception method used by the patient; by signing the Informed Consent Form, the patient agrees to use one of the recommended contraception methods (by the protocol) during the trial and 1 month after the trial completion.

Primary documents must contain data on the sex, age, race, and ethnicity of the patient. A height meter is used to measure the patient's height in centimeters, the weighing scales—body weight in kilograms.

The anthropometric examinations will be conducted in accordance with the Health Risk Monitoring (EHRM) Recommendation for indicators, international collaboration, protocol and manual of operations for chronic disease risk factor surveys, 2002 (17).

Height should be measured in all the patients (the causes which make the height measurement impossible include hair-style peculiarities (e.g., mohawk), patient's refusal to take off a headwear (e.g., turban), patient's incapacity to stand, exceedance of the height meter's scale). The height meter is a vertically positioned panel with a centimeter division with a sliding horizontal ruler. A standard error must not exceed 2 mm. The patient will be asked to take off his/her shoes, thick clothes, hairpins, or other hair accessories. The patient must touch a vertical panel with his/her hindhead, back, buttocks, calves, and heels (the toes are stuck together). Upper boundary of the external ear canal must be at the same level with lower boundary of the orbital cavity (the jugal bone). The patient will be asked to look forward. If the patient's height exceeds that of the Investigator, the latter should use a platform. A height meter's ruler is put on the patient's head, the scale's divisions are counted. The height must be recorded while the patient is still standing under the ruler. An error must not exceed 0.5 cm.

The patient's weight must be measured in the morning in the fasting condition, after urination and defecation, in the underwear (with further subtraction of an average underwear weight). The weighing scales must be horizontally positioned on a solid ground. An error must not exceed 0.2 kg. The patient should stand in the center of the weighing scales on the both legs. If the weight measurement is impossible, the Investigator should not record any values based on the patient's claims.

4.2.3.2.2 Physical examination and vital signs evaluation

Physical examination will be conducted according to the general rules of the propedeutics of internal diseases: general visual examination, inspection of the mucous membranes, including pharyngoscopy, lymph nodes palpation, evaluation of bones and muscles, palpation, percussion and auscultation of the main organ systems (cardiovascular, respiratory, gastrointestinal, urinary systems) will be conducted sequentially.

Vital signs (HR, BR, BP, body temperature) will be evaluated before the physical examination at rest (after 15 minutes of rest, not earlier than 1 hour after smoking or 2 hours after meal). Heart rate (HR) will be measured during the heart auscultation in parallel with a pulse rate determination on the radial artery (or carotid artery in case the radial artery pulse is weak) for 1 minute in a sitting position; in case of a pulse deficiency, the both parameters should be recorded: HR and pulse rate. Breathing rate (BR) will be measured for 1 minute at rest, in a sitting position, observing breathing movements of the thorax and abdominal wall without drawing the patient's attention.

Blood pressure (BP) will be measured on the brachial artery, in a sitting position, by Korotkoff method, using a certified sphygmomanometer or tonometer with a cuff adjusted for the patient's shoulder in length and width according to the recommendations for measurement (RMOAG/VNOK, 2010). The cuff's size should correspond to the arm's size: a cuff rubber part to be inflated should cover not less than 80% of the arm circumference; a cuff 12–13 cm in length and 30–35 cm in width (medium size) should be used for the adults; although, the bigger and smaller cuffs might be required for bigger and smaller arms, respectively. Before the measurement start, a mercury column or a tonometer needle must be in a zero position. To measure BP on every arm not less than 2 measurements with a 1-minute interval are required; in case of BP difference ≥5 mm Hg, an additional measurement should be made; the lowest result based on the 3 measurement should be recorded as a final one.

Measurement procedure:

- Pump up the air into the cuff fast to the pressure level 20 mm Hg exceeding a common systolic BP (by the pulse disappearance).
- An error must not exceed 2 mm Hg.
- Reduce the pressure in the cuff at a rate of 2 mm Hg per second.
- A pressure level when the 1st tone appears corresponds to a systolic BP (phase 1 of Korotkoff sounds).
- A pressure level when the tones disappear corresponds to a diastolic BP (phase 5 of Korotkoff sounds); in children, adolescents, and young people after physical exertion, in pregnant women, as well as in some disorders in adults when phase 5 cannot be determined, a healthcare practitioner should try to determine phase 4 by significant tones weakening.

- If the tones are very weak, the patient should raise his/her hand and make several compressions by hand, after which the measurement should be repeated without a strong compression on the artery by a phonendoscope membrane.
- BP should be measured on both hands at initial examination only; further measurements must be performed at the hand with higher values.

Body temperature must be measured by the same thermometer type (mercuric or electronic) and method (axillary temperature) throughout the trial.

4.2.3.2.3 Fill-in of TSS questionnaire

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 used at screening to evaluate for a subject's eligibility and baseline evaluation; at Visit 2 (Day 4), to measure efficacy of the trial therapy in the both groups; to evaluate the disease outcomes on Visit 2 (Day 4) and/or Visit 3 (Day 5), where applicable.

4.2.3.2.4 Evaluation of the throat pain intensity according to VAS

The patient will fill in the VAS to evaluate for the throat pain intensity at every visit to the trial site (Visit 1, Visit 2, and Visit 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). The scale is provided in Appendix 5 to this protocol.

4.2.3.2.5. Global evaluation of therapy tolerability by the patient and the physician

Global evaluation of study drug tolerability should be made by the patient and Investigator 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).

4.2.3.2.6 Laboratory tests

The blood for analysis will be collected in the morning, in the fasted state (10–12 hours after the last meal) from the cubital vein by a disposable sterile syringe under aseptic conditions. Approximately 12 ml (1 tablespoonful) of blood will be collected at Visits 1 and 2 (or 3, where applicable).
Hematology (Hb, RBC, WBC, WBC differential, ESR) and biochemistry (total protein, ALT, AST, total bilirubin) will be conducted at the trial site laboratory. Pregnancy urine testusing test strips (immunochromatographic assay of beta-chorionic gonadotropin in the urine) must be performed for all women with the preserved childbearing potential at the screening visit.

4.2.3.2.7 Electrocardiography

ECG will be performed at Visit 1 and Visit 2 or 3 (where applicable). ECG includes electrocardiogram tracing in 3 standard and 3 augmented leads (from the extremities), as well as 6 chest leads at rest in the

lying position. ECG will be interpreted by cardiologist, therapist, or functional diagnostics specialist.

4.2.4 Trial stages

4.2.4.1 Screening/randomization/therapy initiation (Visit 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;
- 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).

4.2.4.2 Efficacy evaluation visit (Visit 2, Day 4)

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 $\leq$ 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 Group A patients (Angal) 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;

4.2.4.3 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.

4.2.4.4 A follow-up visit (Visit 4)

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.

4.2.4.5 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 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 $\leq$ 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).

4.2.4.6 Visit of premature discontinuation of the trial

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

4.3 Subjectivity minimization/elimination measures

4.3.1 Randomization

This will be an open, randomized trial. Every screened patient will be assigned with an individual registration number containing the initials (name, patronymic, surname) and a participant's number assigned to every new screened patient in a three-digit format (001, 002, etc.). The patients who meet the inclusion criteria at the screening visit will be randomized to a study drug group or a comparator drug group using the envelope method. For the purpose of randomization, a list of randomization numbers for the envelops will be generated, every number will correspond to a study drug group or a comparator drug group.

4.3.2 Blinding methods

This trial will be conducted without blinding (an open trial).

4.4 Description of the drugs used in the trial

4.4.1 Dosage form

Study drug: Angal, lozenges [menthol], 1 mg + 5 mg. White to off-white, round, slightly mottled lozenge.
Comparator drug: ANTI-ANGIN® FORMULA, lozenges, 0.2 mg + 2 mg + 50 mg. Lozenges: flat, round, with beveled edges and rough surface, of pink to pinkish-red color, with a specific odor. Color non-uniformity, presence of air bubbles in a high-boiled sugar mass, and insignificant edge irregularity are allowed.

4.4.2 Packaging

Study drug: Aluminum and PVC/PCTFE foil blister. 24 lozenges (2×12) in a carton pack.
Comparator drug: Lozenges. 10 lozenges in AL-PVC blister; 3 blisters in a carton pack.

4.4.3 Labeling of the study drugs

As this is an open trial, the trial site will be provided with the packed products from the series commercially available in the EU (study drug) and Russia (comparator drug). Every carton box with the drugs will contain a self-adhesive label with the data listed below:

- "For clinical trials only";

- A protocol number;
- Title, address, and phone number of the trial site;
- Title, address, and phone number of the trial Sponsor;
- A field for a patient's randomization number.

The label should not overlap the drug name, active substances, and their strength, shelf life, manufacturer's name.

At the screening visit, every patient in the study drug group will be given 2 packages of Angal (48 lozenges), and every patient in the comparator drug group will be given 1 package of ANTI-ANGIN® FORMULA (30 lozenges). The dispensed amounts are sufficient for completion the trial according to the protocol. An excess of the drugs is envisaged for the cases of loss of some lozenges.

4.4.4 Strength and dosage regimen of the study drugs

Angal, lozenges [menthol], 1 mg + 5 mg (Sandoz d.d., Slovenia), the study drug, will be used according to Prescribing Information, 1 lozenge with a not less than 2-hour interval, up to 6–10 times per day, for 4 days or until full recovery (total TSS $\leq$ 2) (whichever occurs first during 4 days of therapy). A single dose of Angal is 1 lozenge. The lozenges are intended for full dissolution in the oral cavity. One lozenge is slowly disintegrating in the mouth.

ANTI-ANGIN® FORMULA, lozenges, 0.2 mg + 2 mg + 50 mg (OOO Valeant, Russia), the comparator drug, will be used according to Prescribing Information, 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (total TSS $\leq$ 2) (whichever occurs first during 5 days of therapy). One dose of ANTI-ANGIN® FORMULA is 1 lozenge. The lozenges are intended for full dissolution in the oral cavity. One lozenge is slowly disintegrating in the mouth.

4.5 Expected duration of the subjects' participation in the trial

Screening period: 1 day;
Treatment period: up to 5 days (including the screening/randomization day);
Follow-up period: up to 2 days.
A maximum duration of each subject's participation: 7 days. A minimum duration of each subject's participation: 6 days (depending on the arm).

4.6 Description of rules for termination of the trial parts or the trial as a whole

The trial may be terminated on the following grounds:

1. Upon the Sponsor's initiative: availability of new toxicological or pharmacological data, or data on SAE which require re-consideration of the previous evaluation of the benefit/risk ratio.
2. Upon the Sponsor's initiative: AEs incidence or severity require the trial termination.
3. Upon the Sponsor's initiative: other reasons including administrative ones.
4. Upon the decision of the regulatory authorities.

The trial may be terminated at a specific trial site in case the patients enrollment or data quality are unsatisfactory, or it is reasonable to assume a breach of GCP and/or Declaration of Helsinki, or other serious protocol deviations.
In case of early termination of the trial, the Sponsor must inform the trial site personnel as well as regulatory authorities with indication of the reason thereof. The rules for trial termination for every participant are described in Section 5.3.

4.7 Record keeping procedures for trial products

The trial sites will be provided with the drugs (the study drug and comparator drug) in the amounts enough for the trial completion, taking into account the planned number of patients to be screened. An authorized trial site specialist shall keep a logbook for the drugs where the drugs receipt to the trial site, dispensing to the subjects, and return of the unused drugs are noted. Storage conditions must be also noted. The study drugs may be used for the purposes of this clinical trial only.
Authorized representatives of the Sponsor or regulatory authorities may check the drugs logbook or availability of the drugs at stock during the trial site audit/monitoring. The drugs must be stored under the required conditions in a room with an access for the authorized personnel responsible for the drugs dispensing only.

4.8 Storing and unblinding of randomization codes

This is an open trial. The Sponsor will keep a list of the randomization codes. The trial sites will be provided with the sealed envelopes containing randomization numbers. The envelopes must be opened

sequentially, from the smaller numbers to bigger ones, to avoid a breach of a randomization principle.

4.9 A list of all the data to be recorded in eCRF

All the data obtained during this clinical trial will be considered to be primary data and subject to record in eCRF.

5 Selection and exclusion of the subjects

5.1 Inclusion criteria

The patients who meet all the inclusion criteria listed below will be included in the trial:

1. The Informed Consent Form voluntarily signed by the patient.
2. Men and women at the age of 18 to 45 years old, inclusively.
3. A diagnosis of acute, uncomplicated, inflammatory and infectious condition of the pharynx associated with the inflammation and pain in the throat.
4. Manifestation of the first signs of acute, uncomplicated, inflammatory and infectious condition of the throat (pharyngitis and/or tonsillitis) not more than 48 hours before the inclusion.
5. A baseline total sum of TSS (Tonsillopharyngitis Severity Score) points ≥5.
6. Body temperature measured in the axillary cavity is less than 37.5 °C.
7. Women with childbearing potential should demonstrate a negative pregnancy test result at screening (except for the women after surgical sterilization or menopause for more than 2 years) and use the established contraception methods for at least 3 months before the initiation of the trial therapy and 1 month after completion of the trial.
8. Men should use adequate contraception during the trial, since signing of the Informed Consent Form and till the trial completion, and for 30 days after the trial completion.
9. Ability to understand the presented information on the clinical trial, readiness to comply with the protocol, ability to use the study drugs by oneself and evaluate the symptoms according to VAS (visual analogue scale) or other questionnaires according to the protocol.

5.2 Non-inclusion criteria

The patients who comply with at least one of the criteria listed below will not be included:

1. Prior tonsillectomy, tonsillotomy.
2. Chronic conditions of the nasopharynx or oropharynx, ulcerative oral disorders.
3. History of hypersensitivity or allergic reactions to any components of the study drugs or local anesthetics.
4. Use of analgesics during less than 12 hours before the trial start and/or impossibility to discontinue the analgesics for the trial period.

5. Use of antibiotics during less than 48 hours before the trial start and/or planned use of antibiotics during the trial.
6. Use of topical drugs (aerosols, gargle solutions, fast-disintegrating tablets/lozenges/pastilles) in the pharynx during less than 12 hours before the trial start and/or impossibility to discontinue topical drugs, except for the study drugs, for the trial period.
7. Use of the systemic, inhalation, or nasal glucocorticosteroids during 30 days before the trial start and/or planned use of the glucocorticosteroids (except for the topical skin drugs) during the trial.
8. Impossibility to discontinue other drugs which might influence the trial results, e.g. antiviral or prohibited concomitant drugs (see *Prohibited concomitant therapy* section), for the trial period.
9. Signs of a primary bacterial pharyngitis or secondary bacterial infection (including body temperature increase above 37.5 °C, purulent pharyngeal pellicles, significant intoxication, leukocytosis, neutrocytosis, WBC differential's shift to the left (increase in stab neutrophils, presence of younger neutrophils), ESR more than 30 mm/h).
10. Granular pharyngitis.
11. Signs of rhinitis, sinusitis, otitis, eustachitis, laryngitis, tracheitis, bronchitis (such conditions require therapy which might influence the trial results).
12. Phenylketonuria.
13. Deficit of saccharase or isomaltase (according to anamnesis data).
14. Glucose-galactose malabsorption (according to anamnesis data).
15. Fructose intolerance.
16. Diabetes mellitus.
17. Glucose-6-phosphate dehydrogenase deficiency (according to anamnesis data).
18. Hemochromatosis.
19. Anemia (Hb less than 120 g/l according to hematology test).
20. Hyperoxaluria.
21. Urolithiasis.
22. Myasthenia.
23. Severe, uncontrolled, cardiovascular condition which, in the Investigator's opinion, preclude the patient from participation in the trial, namely:
    a. Severe (IV acc. to Canadian Cardiovascular Society) or unstable angina;
    b. Decompensated chronic heart failure (NYHA stage IV);
    c. Myocardial infarction for the last 6 months;
    d. uncontrolled arterial hypertension (BP more than 180/115 mm Hg).

24. Pregnant and/or breastfeeding women.
25. Participation in other clinical trials at the screening visit or for 30 days before the screening visit.
26. Surgical intervention for 30 days before the screening visit or planned surgical treatment during the trial (sooner than a follow-up visit is completed), including diagnostic procedures or hospital stay.
27. Known or suspected narcotic/alcohol abuse.
28. A suspected low compliance or incapability of the patient to perform the procedures and comply with restrictions according to the trial protocol (e.g., due to mental disorders).
29. Any cardiovascular, renal, hepatic, gastrointestinal, endocrine, or nervous disorders, or any other conditions/diseases which, in the Investigator's opinion, might inflict harm to the patient's health.

5.3 Exclusion criteria

5.3.1 Terms and conditions for the subjects' exclusion from the trial

The subjects may be excluded from the trial on their own free will at any moment, without giving any reason, as well as upon decision of the Investigator or Sponsor in cases when continuation of the participation may inflict harm to the patient's health and/or life. In addition, the patient must be excluded in the cases listed below:

1. Negative course of the disease with signs of the secondary bacterial infection (including body temperature increase above 37.5 °C).
2. The Ethics Committee, regulatory authorities, or Sponsor terminate the trial or participation of the specific trial site for any reason.
3. The Investigator's decision to withdraw the patient from the trial in the interests of the patient.
4. Withdrawal of the informed consent (unwillingness of the patient to continue his/her participation in the trial).
5. Serious deviation from the trial protocol.
6. Individual intolerance of the study drugs.
7. Clinically significant adverse event or serious adverse event.
8. Patient's non-compliance.
9. False inclusion (e.g., the patient was included in breach of the inclusion/non-inclusion criteria).
10. The patient complies with the non-inclusion criteria during the trial.
11. The patient receives or requires an additional therapy which might influence the trial results or patient's safety (see *Prohibited concomitant therapy* section).

12. Other conditions or events which, in the Investigator's opinion, require the patient's exclusion from the trial.

5.3.1.1 Terms and volume of data on the excluded subjects

In case of trial discontinuation on the subject's free will, the Investigator should make effort to find out the reason thereof. In case of trial discontinuation due to AEs/SAEs, the subject should be followed-up until the AEs/SAEs are resolved. In case of discontinuation from the trial prematurely, the patient should visit the trial site for early discontinuation procedures (as an unscheduled visit); if the patient refuses to visit the trial site, he/she should be contacted by phone with recording of all available information.

5.3.2 Terms and conditions of suspend or discontinuation of the trial therapy

The patients may stop taking the study drugs according to the protocol or upon withdrawal from the trial.

5.3.3 Replacement of the excluded subjects

Replacement of the excluded patients during the trial is not envisaged.

5.4 Acceptable contraception methods

The patients must follow adequate contraceptive methods throughout the trial as well as within 30 days after its completion.
Effective contraception methods include:

- True abstinence;
- Oral contraceptives (combination drugs containing progestogen, or progestogen alone);
- Injectable progestogen;
- Levonorgestrel implants;
- Estrogen-containing vaginal ring;
- Transdermal contraceptive patches;
- Intrauterine device (IUD) or intrauterine system (IUS) meeting the efficacy criteria according to Prescribing Information;
- A male partner has been sterile (vasectomy with documented azoospermia) prior to inclusion of a woman, provided that he is the only partner of the female patient. For the purpose of this definition, "documented" is related to the result of a patient's medical examination by the Investigator/responsible person or a patient's past medical history review for evaluation of eligibility for

inclusion, obtained during the interview with a patient or from his/her medical records.

- Double barrier method: a condom or an occlusive cap (diaphragm or cervical/vault caps) with a spermicide (foam/gel/film/cream/suppository).

Men should use adequate contraception during the trial, since signing of the Informed Consent Form and till the trial completion, and for 30 days after the trial completion.

6 Trial therapy

6.1 Therapy regimens

The study drug group (Angal, lozenges [menthol]): 1 lozenge, as needed, up to 6–10 times per day, for 4 days or until full recovery (total TSS ≤ 2) (whichever occurs first during 4 days of therapy). A single dose of Angal is 1 lozenge. The lozenges are intended for full dissolution in the oral cavity. One lozenge is slowly disintegrating in the mouth.
The comparator drug group (ANTI-ANGIN® FORMULA, lozenges): 1 lozenge with a not less than 2-hour interval, up to 6 lozenges per day, for 5 days or until full recovery (total TSS ≤ 2) (whichever occurs first during 5 days of therapy). One dose of ANTI-ANGIN® FORMULA is 1 lozenge (keep in the mouth till full dissolution). The lozenges are intended for full dissolution in the oral cavity. One lozenge is slowly disintegrating in the mouth.

6.2 Allowed and prohibited therapy

6.2.1 Allowed prior and concomitant therapy

All concomitant therapies except for those stated in Section 6.2.2 are allowed.

6.2.2 Prohibited prior and concomitant therapy

The drugs listed below are prohibited for use throughout the trial period:

1. Topical drugs (aerosols, sprays, inhalations, gargle solutions, fast-disintegrating tablets/lozenges/pastilles) in the pharynx or nose.
2. Systemic, inhalation, or nasal glucocorticosteroids.
3. Systemic or topical (intranasal or pharyngeal) antibacterial drugs.
4. Anti-viral drugs.
5. Immunomodulatory agents.
6. Painkillers or antipyretic agents.
7. Class I antiarrhythmics.
8. Cholinesterase inhibitors (including neostigmine, distigmine, pyridostigmine) and other drugs for myasthenia.

6.3 Methods to monitor the subjects' compliance with trial procedures

At every visit after Visit 1, the subjects' compliance will be checked by counting the unused drug and analysis of the patient's diaries. It should be noted that the drugs doses stipulated by the protocol are 6 to 10 (maximum) lozenges per day (Angal),

and to 6 lozenges per day with at least 2-hour interval (ANTI-ANGIN® FORMULA). The both drugs should be taken when needed (a sore throat).
In view of the nature of drug intake (when needed), the lower margin of compliance will not be evaluated; the number of used lozenges is compared to maximum amounts stated in the protocol for the study drug (up to 10 lozenges per day for Angal) or Prescribing Information for the comparator drug (up to 6 lozenges per day for ANTI-ANGIN® FORMULA).

7 Efficacy evaluation

7.1 List of efficacy parameters

Primary outcome measure

The primary outcome measure was the percentage of patients **without sore throat after 3 days of therapy on Day 4, as** evaluated by the Investigator according to the Tonsillopharyngitis Severity Score (TSS), in both Angal and ANTI-ANGIN® FORMULA arms.

Secondary outcome measures

The secondary outcome measures in the both therapy groups were:

- The frequency of ≥50% total score reduction according to the TSS questionnaire completed by the Investigator as compared to the baseline in both Angal 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 disease symptoms relief, 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.

7.2 Methods and timing for evaluation, recording, and analysis of efficacy parameters

The methods for efficacy criteria evaluation are described in Section 4.2.3.2. The first endpoint is evaluated in the morning at Visit 2 (Day 4, after 3 days of the trial therapy) before the study drugs intake. Other efficacy endpoints are evaluated in terms stated in Section 7.1.

8 Safety evaluation

8.1 List of safety parameters

The following parameters will be taken into account for the safety evaluation:

- AEs and/or SAEs rates per trial arms;
- Global tolerance evaluation during the trial by the Investigator and patient;
- Vital signs (heart rate, blood pressure, body temperature, breathing rate);
- ECG parameters;
- Laboratory results.

8.2 Methods and timing for evaluation, recording, and analysis of safety parameters

Safety parameters are evaluated at every planned and unscheduled visit.

8.3 Requirements for reporting, registration, and reporting of AEs and intercurrent diseases

8.3.1 Definitions of adverse events and serious adverse events

Adverse event (AE) is any adverse medical event identified in a patient or a clinical trial patient after the use of the drug, which may or may not have a causal relationship with its usage. Thus, adverse event (AE) can represent any adverse symptom (including laboratory deviation from the norm), complaint, or disease, for which a temporal causal relation cannot be excluded with the use of medicinal (study) product, regardless of the presence or absence of such a relation.
Serious adverse event (SAE) represents any event, unfavorable from medical perspective, which with any dose:

- Resulted in death;
- Is life threatening;
- Results in disability/incapacity to work;
- Is a congenital anomaly or development defect;
- Requires hospitalization or its extension;
- Is significant from medical perspective: a decision whether expedited reports is feasible in other situations (e.g., in case of events important from medical perspective, which are not directly life-threatening for a

patient, do not result in death or hospitalization, but pose the patient to risk or require intervention to prevent one of the above outcomes) shall be made on the basis of medical and scientific evaluation. Such cases should be usually considered serious adverse events.

Adverse drug reaction (ADR) is any adverse event which might have causal relation to the drug in the opinion of the Investigator or Sponsor (see Section 8.3.3 below).

An unexpected adverse reaction is defined as an adverse drug reaction, the nature or severity of which is not consistent with the Reference Safety Information (e.g. SmPC, Investigator's Brochure). The term "severity" is used to describe the intensity of a specific event. This term should be distinguished from the term "serious". Reports which add significant information on specificity, increase in incidence, or severity of the known, already documented serious adverse reactions, constitute the unforeseen events.

Information about side effects already known for this study drug is available in the Investigator's Brochure. This information will be included into Patient Information Sheet, and it should be discussed with the trial subjects.

More details are given in Brief Reference Manual for filling in the Serious Adverse Event Report Form (to be provided by the Sponsor).

8.3.2 Intensity of AE

The term "severity" is used to describe the intensity of a specific event. This term should be distinguished from the term "serious". During the trial, the Investigator will detect adverse events and classify them by intensity as follows:

- Mild event: as a rule, is temporary and does not restrict normal daily activities;
- Moderate event: restricts normal daily activities significantly;
- Severe event: impedes normal daily activities in full.

8.3.3 Causality with the study drug

The Investigator will perform evaluation of adverse events after examination of all available data. In addition, he/she will perform their repeated evaluation if new information appears. The study drug is the drug investigated during the trial, and control drug or placebo used during any phase of this trial.

All AEs spontaneously reported by volunteers or observed by the Investigator will be evaluated in accordance with the following definitions:
Suspected: temporal relation between development of clinical event and applied study drug indicates **possible presence of causality,** while other drugs, therapeutic interventions, or baseline states do not allow explaining development of this event with sufficient grounds.
Non-suspected: temporary relation between development of clinical event and used study drug **indicates for the remote presence of causality**, while other drugs, therapeutic interventions, or baseline states can be considered with sufficient grounds as explanation for observed event.
Evaluation of causality is of great significance, and it should be performed for each reported unique event and for each study drug, not being the study drug or any other concomitant drug (if appropriate). In case of no evaluation of causality available, the Sponsor will consider such events as associated with the trial therapy.
The Investigator must inform LPPV on AEs with suspected causality to the drug which is not a study drug or another concomitant drug (produced by Sandoz or other manufacturers), even if those AEs are not serious (see Section 8.3.5 for contact information).

8.3.4 Documentation on adverse events

Any AE (not serious or serious), occurring after the subject has provided informed consent specific for this trial before completion of the trial, must be documented on the pages intended for adverse events in the Individual Case Record Form (ICRF).
The non-leading questions to the subjects should be used at each trial visit in order to detect AE. AEs can be also detected if the subjects report on them themselves during visits or between the visits as well as if they are found during examination, by the results of laboratory analyses or other tests. All AEs require proper treatment. Actions taken to cure AE should be documented and related to one of the following categories: "no action taken", "prescription of the drug (accompanying therapy)", or "other treatment". Besides, the actions should be documented, which were undertaken in relation to the study drug, and they should be referred to one of the following categories: "no changes", "withdrawal", "dose reduced", "dose increased", "therapy suspended", "action is unknown", and "not applicable". Concomitant therapy, other treatment methods, or changes of the study drug should be determined and documented.

The medical conditions/disorders present before the trial therapy initiation are considered to be AEs unless they get worsened after the inclusion in the trial. Abnormal laboratory or test results are considered to be AEs only if they evoke clinical signs, are clinically significant, or require therapy.
After detection of AE, it should be followed up until its resolution or until it is recognized as permanent. The event outcome should be documented and referred to one of the following categories: "event not resolved/did not change", "health status gets worse", "event resolved/subject recovered", "event improved/subject recovers", "event resolved/subject recovered with complications", "lethal outcome", or "outcome unknown". Evaluation of AE should be performed during each visit (or more frequently, in case of any indications) for any changes in severity, suspected association with the study drug, interventions undertaken for its treatment, and outcome.

AE in the interval between signing of informed consent and administration of the first dose

Any AEs, which occurred in the interval after signing of informed consent specific for this trial and before administration of the first dose, should be documented as screening period events. Moreover, the results of evaluation of the association with the study drug should be documented as follows: "study drug was not administered yet".

AE after the first dose of the study drug

The Investigator should follow up all the AEs occurred since the first intake of the drug and during the trial, till the last visit of the subject when the event outcome is evaluated for the last time with further recording in eCRF.

SAEs not resolved as at the last visit

If SAE is not resolved as at the last visit, the Investigator should follow up the subject till SAE resolution or stabilization/shift to a permanent stage (for SAEs with a suspected relation to the study drugs) or during up to 30 days since the last visit for SAEs without suspected relation to the study drugs.
The Investigator must report on the SAE follow up as per the Reports on SAEs, Section 8.8.5. below.

SAEs registered after the last visit

At the last visit, the Investigator should instruct each subject to report on any new SAEs (outside a follow-up period according to the protocol) which, in the subject's opinion, might be associated with the study drugs. The Investigator must inform recipients on SAR as per the Reports on SAEs, Section 8.3.5. below.

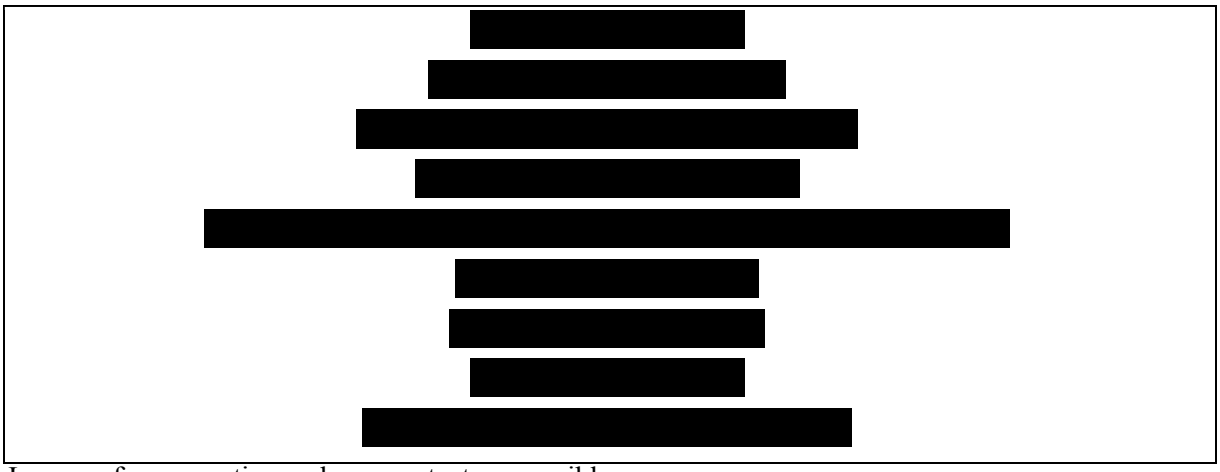
Clinically relevant abnormal laboratory results at the last visit

The Investigator must document the clinically significant, abnormal laboratory results revealed at the last visit as AEs even without any relation with the specific study drug.

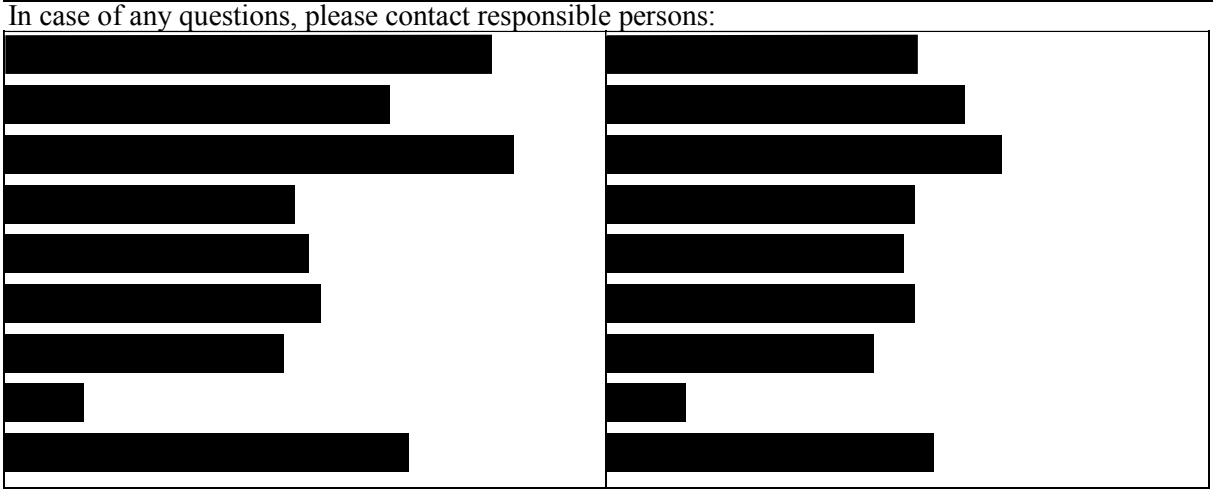
8.3.5 Reports on SAEs

The Investigator must immediately (not later than 24 hours since the receipt of data on SAEs) report any SAEs even in case the Investigator considers these SAEs not related to the study drugs.
The Investigator must use Novartis Serious Adverse Event Report Form to report on SAE for initial or subsequent reporting. The form should be forwarded by fax or email to LPPV with a copy to a manager responsible for the trial (Sponsor/CRO) using the contact information given in a table below.
The Investigator must forward all the updates/new information in a separate Serious Adverse Event Report Form as a follow-up regarding the previously reported SAE. Such information must dwell on recovery or continuation of SAE, diagnosis (if any), therapy details (if any), continuation or discontinuation of that subject from the trial.
Repeated episodes, complications, or progression of the initial SAE should be reported as a follow-up for the original episode, irrespective of the event time.
Any new SAE, which is considered as completely unrelated to previously reported one, shall be reported as a new and separate event.
The Investigator should answer any questions from LPPV, CRO, or Sponsor regarding SAEs reporting within 24 hours.
For more detailed information, refer to the Quick Reference Guide for Completing the SAE Form.
The Investigator should keep the notifications on information delivery to all the recipients in a separate file.

Contact information for SAE reporting



In case of any questions, please contact responsible persons:



Notification of the Investigators and the 6-month line listings

If a serious adverse drug reaction (ADR) is not listed in the reference safety information (e.g., SMPC, Investigator's Brochure), the Sponsor may request for an urgent additional information from the Investigator for reporting to the health authorities.

The Sponsor is entitled to, where applicable, forward notifications for the Investigators and the 6-month line listings of SUSARs (not previously reported) to all the investigators associated with any trial of the same study drug.

The Investigator or CRO (as envisaged in the trial agreement) must submit the notifications for Investigators and the 6-month line listings, if applicable, to Local Ethics Committees (LEC)/Ethics Councils. CRO must submit the notifications for Investigators and the 6-month line listings, if applicable, to the Ethics Council under the Ministry of Health of Russia.

Reporting to health authorities

The Sponsor shall submit all the reports to relevant regulatory authorities within the specified timelines.

Training of investigators

By signing the trial protocol, the Principal Investigator confirms that he/she has passed the training held by CRO and got familiarized with the Sponsor's requirements and his/her responsibilities on reporting the AEs/SAEs and pregnancies as defined in the trial protocol.

8.4 Pregnancy cases

The Investigator must immediately (not later than 24 hours since the receipt of information on pregnancy) inform the Sponsor/LPPV with a copy to a manager responsible for the trial (Sponsor/CRO) as described in Section 8.3.5 on all the pregnancy cases occurred during the trial. Pregnancy reports are registered since the first intake of the study drug only.

The Investigator must exclude the pregnant subject from the trial immediately; this pregnancy should be monitored to determine its termination, including spontaneous or planned abortion, details on delivery and on presence or absence of any development defects, congenital anomalies, or complications in infant's mother and/or in a newborn.

If the Investigator becomes aware of pregnancy of the sex partner of male participant of the trial, which was started with high probability during participation of this man in the trial (i.e., during exposure of the child's father organism to the drug), these pregnancy cases should be also reported after receipt of informed consent from (expecting) mother.

The pregnancy cases should be registered in the Clinical Trial Pregnancy Form. Additional information about pregnancy should be registered in the same form. Moreover, it must include possible relation of any termination of pregnancy to use of the study drug.

Any SAE noted during pregnancy should be reported using SAE Report Form as described in Section 8.3.4.

For more information, see the Clinical Trial Pregnancy Quick Reference Guide; Novartis document.

8.5 Quality complaints

In case of quality complaints (technical or transportation claims), the Investigator must report to the Sponsor thereon within 24 hours after receipt of information as described in Appendix 2. Any AE associated with the quality complaints shall be documented and reported as described in Sections 8.3.4 and 8.3.5.

8.6 Special cases

Special cases may be serious or non-serious (see below) and must be reported as AEs pursuant to Sections 8.3.4 and 8.3.5 even in absence of other AEs associated with the special cases.

A special case scenario	**The Investigator must inform LPPV**
Exposure during breastfeeding	X
Intentional overdose by the patient (including the suicide attempts which are always considered to be serious)	Only if associated with SAE
Drug interactions	Only if associated with SAE
Withdrawal response/syndrome	Only if associated with SAE
Drug dependency, misuse, abuse, or addiction (always serious)	X
Suspected transmission of infectious agents (always serious)	X
Death (always serious even without other events)	X

8.7 Information verification

Verification of information between a safety database of the Sponsor and a clinical database stored in CRO will be performed at the end of the trial according to a verification plan by comparison of the relevant summary tables from the both databases.
During data processing, eCRF/information in the clinical database will be reviewed for potentially unreported SAEs. Any potential SAE requires an exact match in the following parameters between the clinical database and safety database: trial number, center number, subject number, randomization number, study drug, degree of severity, date of death (if applicable), and causality according to the Investigator's evaluation. All other parameters must be credible and consistent from medical perspective. A thorough verification of information must be performed for every event subject to reporting as well as any other events of special interest (if applicable) considered to be related to the study drug, including dates of the drug use, outcome, medical history, and concomitant therapy.

9 Statistics

9.1 Description of the statistical methods to be used including the terms for every planned interim analysis

Statistical analysis will be performed using R Project specialized software.
The continuous (quantitative) data will be presented as a number of observations, arithmetic mean, confidence interval (CI) 95% for the mean (unless stated otherwise), standard deviation (SD), median, interquartile range (IQR), minimum, and maximum.
The serial, categorical, and qualitative data will be presented as absolute incidences (number of observations), relative incidences (%), and CI 95% (unless otherwise stated).
The concomitant diseases and AEs will be coded using MedDRA terms.
This section contains a brief description of the planned analysis. Full analysis will be presented in the statistical analysis plan.

9.1.1 Demographic and other baseline data (group comparability for the analysis)

All the data obtained in the groups before the trial therapy initiation (demographic, laboratory, instrumental, and physical examinations data, vital signs, etc.) will be compared between the groups to determine the groups' comparability for analysis.
The Fisher's exact test and chi-square will be used to compare the qualitative and serial data, while the t-test or the Mann–Whitney test will be used for the quantitative data (depending on the quantitative data distribution).

9.1.2. Analysis of the primary efficacy endpoint

The primary outcome measure in this trial was the proportion of patients **without sore throat after 3 days of therapy, on Day 4,** as evaluated by the Investigator according to the Tonsillopharyngitis Severity Score (TSS), in both Angal and ANTI-ANGIN® FORMULA arms.
A null hypothesis of this trial assumes that Angal, the study drug, is less effective than ANTI-ANGIN® FORMULA, the comparator drug. An alternative hypothesis of this trial assumes that Angal, the study drug, is not less effective than ANTI-ANGIN® FORMULA, the comparator drug.

14.5% is chosen as a non-inferiority margin (see Section 9.2 for a justification) based on the results of a randomized, placebo-controlled trial of a similar drug.
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).

9.1.3 Analysis of the secondary efficacy 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 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 disease symptoms relief, 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.

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 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).

9.1.4 Safety parameters analysis

A descriptive part of the safety analysis will include an evaluation of incidences and two-sided CI 95% for the following parameters in every trial group:

- AEs: the incidence in total and for separate categories (according to MedDRA), for the trial and by groups;
- SAEs: the incidence in total and for separate categories (according to MedDRA), for the trial and by groups;
- Incidence of clinically significant changes of the physical examination results by visits and groups;
- Incidence of clinically significant changes of the laboratory results by visits and groups;
- Incidence of clinically significant changes of the vital signs (body temperature, BP, pulse rate, HR) by visits and groups;
- Incidence of clinically significant changes of the ECG parameters by visits and groups;
- Global tolerance evaluation during the trial by the Investigator and patient;

The Fisher's exact test will be used to compare incidences between the groups, and chi-square will be used to compare the global therapy tolerability by the Investigator and patient. The McNemar's test will be used to evaluate for the dynamic changes during the trial (before–after) for all the repeatedly evaluated incidences in every group.
In addition to the incidence, all the quantitative safety parameters will be presented in a table form (laboratory data, vital signs, ECG) by visits and groups. The difference will be evaluated using 2-way-ANOVA (group and visit numbers will serve as the relevant factors). The post-hoc criteria will be used in case of significant difference.
Safety analysis will be performed on the safety population.

9.2 Planned number of subjects

A statistical objective of the trial will be an evidence of non-inferior therapeutic efficacy and safety of the study drug Angal comparing to the drug ANTI-ANGIN® FORMULA in the treatment of acute infectious and inflammatory diseases of the pharynx. Justification of a non-inferiority margin is based on the results of a placebo-controlled trial of pastilles with chlorhexidine and lidocaine conducted by [redacted] [redacted] [Kris De Ceulaer. A summary of a clinical trial proves that chlorhexidine/lidocaine lozenges are effective and safe. 11-8-2015].
This trial demonstrated absence of a sore throat (a TSS subscale) 3 days after the therapy initiation, on Day 4, in 37.5% patients in the trial arm and 63.1% patients in the placebo arm.

Table 2. Answers distribution results regarding questions on a sore throat at baseline and Day 4

	Baseline visit		D4	
N	Product N=106	Placebo N=103	Product N=106	Placebo N=103
Sore throat				
Unknown	0	0	2 (N=104)	0
Absent	0 (0%)	0 (0%)	65 (62.5%)	38 (36.9%)
Mild	3 (2.8%)	3 (2.9%)	27 (26.0%)	45 (43.7%)
Moderate	77 (72.6%)	75 (72.8%)	11 (10.6%)	19 (18.4%)
Severe	26 (24.5%)	25 (24.3%)	1 (1.0%)	1 (1.0%)
p	1.0000		0.0016	

Therefore, a lower limit of CI boundary may be calculated for the difference in sore throat presence after 3 days of therapy, taking into account 104 participants and 103 patients.
In view of the considered nosology and absence of significant factors requiring a conservative approach for determination of the

non-inferiority margin, for this purpose we can use a two-sided CI 90%. To calculate a two-sided CI 90%, a method described by Newcombe, Robert G. was used "Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods," Statistics in Medicine, 17, 873-890 (1998). CI 90% will amount to 14.56–36.66%, i.e., the lower limit will correspond to one-sided CI 95%. Therefore, a margin of 14.5% is considered to be justified.

NCSS 8.0 Two Proportions Report
Dataset Untitled
Zero Adjustment Method: None
Note: Exact tests and c.i.'s were not run because total count > 50 (specified under 'Reports' tab).

Table Section

				N1	N2	M1	M2	N
A	**B**	**C**	**D**	**(A+C)**	**(B+D)**	**(A+B)**	**(C+D)**	**(N1+N2)**
65	39	38	65	**103**	**104**	**104**	**103**	**207**

Confidence Intervals of Difference (P1-P2)

Interval Method	**Estimated Value**	**Confidence Limit**	**Confidence Limit**
Chi-Square (Pearson)	0.2561	0.1456	0.3666

(The calculation results are presented in the language of the original source, i.e., from NCSS 8 statistical program).

- This is a *non-inferiority trial;* therefore, ***a non-inferiority margin for the primary endpoint should be justified and amount to not more than 14.5%.***
- An expected rate of positive response to therapy (absence of a sore throat as an efficacy measure) in a comparator drug arm is 63%.
- An expected rate of positive response to therapy (absence of a sore throat as an efficacy measure) in a study drug arm is 65% (chosen within the tested hypothesis and based on the sample size and expected positive response).
- A one-sided type I error (α) = 2.5 % (0.025)
- A type II error (β) = 20% (0.2), which corresponds to 80% power.
- Expected discontinuation from the trial will amount to 10% during the treatment.

The tested hypotheses are worded as follows:

1. Null hypothesis (H_0): Difference in the primary endpoint achievement incidence while using Angal, 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:

$$H_0: p_1 - p_2 \leq -0.145$$

2. Alternative hypothesis (H_A): Difference in the primary endpoint achievement incidence while using Angal, 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

$$H_A: p_1 - p_2 > -0.145$$

Where p_1 and p_2 is the primary endpoint achievement incidence while using Angal, the study drug, and ANTI-ANGIN® FORMULA, the original drug, respectively.

To calculate a sample size in every group, one can use a formula presented by Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 90:

$$n = \left(p_1 \times (1 - p_2) + p_2 \times (1 - p_2)\right) \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{p_1 - p_2 - \delta}\right)^2$$

where:

n = Size of one group;

z = Normal distribution function at the set levels of α and β;

δ = Non-inferiority margin;

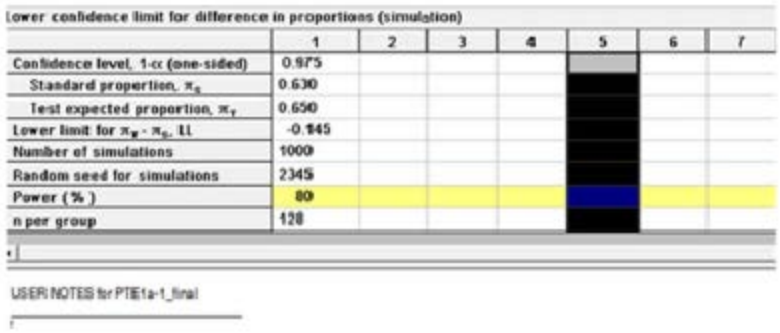
p_1 = Expected proportion in Angal group;

p_2 = Expected proportion in ANTI-ANGIN® FORMULA group.

Substituting the above data into this formula, we obtain a minimal number of patients in every group without account for withdrawal: 128 patient completed the trial (total 256 patients).

In view of the expected discontinuation from the trial during the therapy of 10%, not less than 280 patients are required for randomization (140 patients in each group).

The calculation results by the above formula were also checked using nQuery, a validated program (see below), and considered to be identical.



Lower confidence limit for difference in proportions (simulation)

	1	2	3	4	5	6	7
Confidence level, 1-α (one-sided)	0.975						
Standard proportion, π_S	0.630						
Test expected proportion, π_T	0.650						
Lower limit for $\pi_T - \pi_S$, LL	-0.145						
Number of simulations	1000						
Random seed for simulations	2345						
Power (%)	80						
n per group	128						

USER NOTES for PTE1a-1_final

9.3 Applicable 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 an one-sided statistical criterion will be used with 97.5% significance level (a threshold p value is below 0.025). 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.

9.4 Trial termination criteria

The trial may be terminated under conditions described in Section 4.6 of this protocol.

9.5 Accounting for missed, unanalyzable, and questionable data

During the monitoring visits to the trial sites, the clinical trial specialists (monitors) authorized by the Sponsor will analyze eCRFs for the data completeness. In the case of absence of data on CRFs and availability of relevant information in the primary documentation, questions for investigators and regulations to address inconsistencies will be formulated. 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 might 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, an 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.

9.6 Procedures for reporting any deviations from the original statistical plan

All deviations from an initial statistical plan must be described and justified in a protocol amendment and/or a final trial report (in the last case, a statistical analysis plan developed before the start of a final statistical analysis must contain a list of those deviations with justification for the reasons thereof).

9.7 Selection of subjects for analysis

The following data sets will be used 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 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).
- The safety population (safety): all randomized subjects who received at least one dose of the trial/reference drug and have completed at least one visit to the evaluation of the parameters of safety (i.e., at least all the procedures of 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).

9.8. Interim analysis

An interim analysis may be conducted by the Sponsor's decision after receipt of efficacy data for Angal and ANTI-ANGIN® FORMULA 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 and ANTI-ANGIN® FORMULA drugs.

10 Direct access to primary data/documents

Primary data represent entire information contained in original records and certified copies regarding clinical data, observations, and other measures within the trial scope and which is required for reconstruction and evaluation of the trial. The investigator must cooperate for the purposes of monitoring, audit(s), expert evaluation by the Ethics Council and regulatory authorities and provide the access to the primary data/records.

The primary data must be stored in a proper quality throughout the time stipulated for by the local and international laws, as well as written contracts with the Sponsor company. For each subject included, the Investigator must note in the primary records the fact of such participation as well as the following data: an individual identification code, personal data (full name, address), dates of the drug intake, vital signs, any AEs, trial completion dates, the main reasons for discontinuation (if applicable).

The Investigator is obliged to provide direct access to the primary data and documents for the clinical trial specialists and/or authorized representatives (CRO) of the Sponsor, competent bodies' auditors, representatives of the insurance companies, Ethics Committees.

11 Quality control and assurance

11.1 Trial monitoring and quality control

Regular visits by a clinical trial specialist (Monitor), on request of the Sponsor and according to SOPs, before initiation, throughout and upon completion of the trial contribute to a successful trial conduct and accurate data collection, timely detection of errors, proper documenting of the trial process, protection of the subjects' rights, and consistence with the principles of ICH GCP, Declaration of Helsinki, international and Russian laws. Routine trial monitoring includes:

- Confirmation for the proper conduct and documenting of the informed consent receipt, screening, and inclusion of the subjects in the trial.
- Verification of the data in eCRF and primary medical documents.
- Confirmation for documenting and timely reporting of ARs during the trial.
- Confirmation for compliance of the trial site personnel with the requirements for diagnostic and therapeutic procedures stipulated by the protocol.
- Confirmation for documenting the shipments, storage, distribution, and utilization of the study drug/placebo and trial materials.
- Confirmation for competence of the trial site personnel and external laboratories needed for the trial conduct.
- Confirmation for compliance of the diagnostic and laboratory equipment with the safe use requirements during the trial.
- Confirmation for cooperation of the Investigator with the local Ethics Committee regarding the trial safety and introduction of the protocol amendments agreed upon by the Sponsor.

Provision of a quality control of the trial results by the Sponsor's authorized persons or representatives who keep a trial electronic database, reveal for any inconsistence, data imputed by error, or missing data during the cross check of all eCRFs. In case of any questions or necessity of clarification, a special form (a data clarification request) should be forwarded to the Investigator and satisfied in writing during 7 days since the receipt thereof.
In accordance with the requirements of the legislation, the Sponsor or authorized federal authorities have the right to inspect (audit) the

logistical support and documentation on the trial. The Investigator is obliged to provide direct access to documents and all relevant information to the authorized persons for the audit or inspection.

11.2 Amendments to the protocol

The investigators' signatures on a signature list of the protocol mean a written consent to perform a trial in accordance with this protocol. During the trial, the trial materials may be amended and appended. Such changes and additions are considered to be amendments.
A protocol amendment is a written description of changes or formal clarification of the clinical trial protocol wordings. The amendments may be significant and insignificant. Any protocol amendment, before making effective, must be approved according to the established procedure and SOPs of the Sponsor, regulatory authorities, independent Ethics Committees (under the Ministry of Health of Russia and local ones), and signed by the Investigator.
Order of the Ministry of Health of Russia *On Approval of a Review Procedure of a Message on Necessity to Introduce Amendments to a Protocol of the Clinical Trial of the Drug* No. 775 of August 31, 2010 contains a list of significant/insignificant amendments and a procedure of submission thereof for the expert evaluation.
The protocol amendments are significant if they may influence objectives, organization, methods of the trial, statistical methods of data processing, and patients' safety measures during the trial.
The protocol amendments are insignificant if they may not influence the objectives, organization, methods of the trial, statistical methods of data processing, and measures for patients' safety during the trial.
In case of necessity to introduce changes into this protocol, the Sponsor shall submit a message on necessity to introduce amendments to a clinical trial protocol to the Ministry of Health of Russia. The Ministry of Health of Russia shall consider the submitted documents and decide on approval or refusal to the introduction of changes. The protocol amendments must be stored together with the initial protocol version. A title page of the protocol must contain a number and date of the amendments.

11.3 Protocol deviations

Protocol deviation is intended deviation from approved protocol.
Serious protocol deviation 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/her data from clinical and/or statistical parts of the trial. The deviations not referred to as serious ones shall be considered minor protocol deviations.
Serious protocol deviations should be reported as soon as possible to the Sponsor by the clinical center staff and/or CRO and Monitor (if he/she is in the center). The Sponsor can propose to reclassify the protocol deviation (minor into serious and vice versa) based on the estimate. In such a case, the classification performed by the Sponsor shall prevail and must be communication to CRO together with written rationale. The Sponsor must be informed of minor protocol deviations within 10 business days but before commencement of the next clinical period of the trial or before commencement of a clinical phase/statistical phase.

An exception is represented with minor protocol deviations, which can be included in the draft report on the trial:

- Logistic deviations (in time from the planned blood sampling schedule; follow-up visit outranged from the time limits set up in the protocol due to plans/schedule of the participant etc.).
- Administrative deviations (e.g., change of the name).

In case of enrollment of the fewer number of subjects compared to that planned, CRO should inform the Sponsor who might approve of that. This should not be considered to be a protocol deviation.
Notification and reporting of deviations from the protocol shall be submitted to the regulatory authorities and relevant Ethical Committees in compliance with the applicable requirements/instructions/laws.

Procedure for documentation of protocol deviations

The Investigator or a person assigned by the Investigator must document and explain any deviation from the approved protocol. Notification of the Sponsor on protocol deviation can be transferred verbally in exceptional cases (if immediate action/notification is required), which must be followed with written documenting (e.g., via email; updates on the trial period). All protocol deviations must be described in the final report on the trial.

12 Ethics

12.1 General provisions

This trial will be conducted in accordance with the Declaration of Helsinki of the World Medical Association "Guidelines for Biomedical Research Involving Human Subjects" of 1964 as amended; the Russian National Standard *Good Clinical Practice*, GOST R 52379-2005 of September 25, 2005 adopted by Order of the Ministry of Health of the Russian Federation *On Approval of the Good Clinical Practice Rules* No. 200n of April 1, 2016, Federal Law of the Russian Federation *On Circulation of Medicines* No. 61-FZ of April 12, 2010 (as amended), as well as guidelines of the International Conference on Harmonization, including E6 Good Clinical Practice (ICH E6 GCP).

12.2 The informed consent receipt procedure

Before the inclusion, a subject is provided with written information and verbal clarification on objectives, goals, and methods of the trial, as well as expected benefit and possible risks associated with the participation in the trial. Besides, the subjects must be informed on voluntary nature of the participation in the trial and their rights to refuse to participate at any moment without influence on quality of the provided medical care. While a subject is not obliged to report his/her reasons to terminate his/her participation in the trial, the Investigator should try to find out the reasons without violating the subject's rights. The subject's consent must be obtained before initiation of any of the trial procedures.

Processing of the data gathered during the trial is performed with the maintenance of confidentiality of personal data. The subjects should be made aware of the goals of the planned computed data processing and publication terms (e.g., on medical conferences, in magazine articles, and other publicly open sources), when the data is presented in summary not allowing for the subjects identification.

Subjects should be made aware that the authorized representatives of health authorities and of the Sponsor will have access to their confidential health information for the purpose of monitoring, inspection, and audit. The subjects must receive guarantees of the strict confidentiality and non-disclosure of all personally identifiable information.

An Informed Consent Form (a patient information sheet) should be filled in in duplicates, signed, and dated by the patient and Investigator in their own hands. One copy of the signed Informed Consent Form should be kept in the

Investigator's file, the other copy should be given to the subject.

12.3 Confidentiality and identification of the trial subjects

Personally identifiable information will be kept confidential in observance of the right to privacy and confidentiality protection according to the applicable laws. Personally identifiable information will be kept confidential and may be disclosed only to the extent required by law. On publication of the trial results, confidentiality of the personally identifiable information will be maintained.

12.4 Enrollment of subjects from the vulnerable and special populations

The inclusion/non-inclusion criteria do not envisage for participation of the subjects from the vulnerable populations.
Special populations in this trial include women with childbearing potential who, according to the inclusion/non-inclusion criteria, may participate only upon their consent to use effective contraception during the trial which is stated in the patient information sheet and confirmed by signing of the Informed Consent Form.

13 Data processing and record keeping

All the trial relevant records and documents of the trial site, including those contained in the Investigator's file (eCRFs, Informed Consent Forms, logbooks, subject accounting sheets, etc.), as well as primary medical documentation of the subjects must be stored for 15 years after the trial completion. The trial Sponsor must control for storage and availability of all the trial site materials during a life cycle of the study drug. Archival data may be stored as photocopies, as well as on the optical or electronic data storage devices. The Principal Investigator must inform the Sponsor immediately on the unintentional damage/destruction as well as change of the storage place of the archival data from the clinical trial. A targeted destruction of the archival data may be performed only upon a written permission of the trial Sponsor. As far as the subjects perform visits to the trial sites and the Investigator fills in the eCRFs, the authorized monitors of the Sponsor will verify the data in eCRFs and primary documents. In case of accurate and proper fill in of eCRFs, the Monitor shall retrieve the original eCRFs and forward them to the Sponsor while the copies of eCRFs are left at the trial site. In case of any questions arising during the eCRFs data check on part of a data control manager and/or a biostatistics specialist, all the clarifications and changes will be documented by creating a special form (a data clarification request). Answers for those questions, filled in, signed, and dated by the Investigator, shall be checked by the Monitor; in case of satisfaction, the Monitor shall retrieve the original forms while the copies thereof are left at the trial site. The Investigator must provide the information in confirmation of timely enrollment of the subjects according to the protocol criteria.

The trial must be conducted in accordance with the protocol and applicable Sponsor's SOPs. If the protocol needs to be changed, one should follow a procedure described in Section 11.2 of this protocol.

The Investigator must fill in all the primary medical documents and CRFs for all the included subjects.

The Investigator is responsible for the complete and accurate filling of the CRFs. All the data entered in CRFs must be also recorded in subject's medical records in printed form or in the form of records made by the Investigator or another authorized person of the trial site.

The CRFs, in accordance with the primary documents, should contain all significant information on the subject's participation in the trial. Besides, CRFs should contain data on the trial completion by the subject. The CRF must be filled in not later than 5 days after the subject's visit to the trial site.

The CRF must be filled in in a distinct, readable handwriting by a black pen. The errors must not be corrected over the entry, or erased, or removed with the correction fluid. An error must be strikethrough, with the correct data written on top with a signature, date, and initials of the Investigator. All the missing data must be explained in eCRF, containing a special mark field (check in the box) to confirm for the data omission. If necessary, the reasons for data omission may be explained in eCRF on a comment page with reference to the relevant page. The eCRFs must be signed by the Investigator. Such signatures confirm for the data reliability.

All information relating to the trial and data collected are strictly confidential. The Investigator may disclose the trial information to the parties not directly involved in the trial only upon Sponsor's permission.

A final report containing statistical and clinical reports is compiled after a database lock and completion of statistical processing of the trial results. A final report should be signed by the Principal Investigator of the trial site to confirm for the results and conclusions, and sealed with the institution's seal.

14 Finance and insurance

14.1 Trial financing

The trial is financed by the Sponsor through CRO. The relevant agreements will be concluded between CRO and every trial site before the trial initiation.

14.2 Trial subjects insurance

The Sponsor must provide for insurance of health and life for the trial subjects. The patients will be reimbursed in case of harm, a threat to life or health resulted from the study drug or comparator drug use according to the applicable law.

15 Publications

15.1 General provisions

The information contained in this document is the property of the Sponsor, and its transfer to third parties is allowed only with the written permission of the Sponsor. This information may be accessed only by the investigators and the trial site personnel, members of the independent Ethics Committee, or health authorities responsible for the clinical trial control. Information about the trial, to the extent necessary to make a decision about provision of consent to participation, shall be provided to the volunteers, whom the Investigator plans to include into the trial.

15.2 Publication and use of the trial results

The exclusive rights for this trial results belong to the trial Sponsor. No data from this trial may be presented or published without a prior written permission of the Sponsor.

16 Appendices

16.1 Appendix 1. Quality complaints

Definitions

Quality complaints are the complaints to the study drug or reference drug and include:

- Technical complaints are the complaints associated with drug/medical device quality and include the following:
  - Any defect in quality and/or effectiveness, e.g., change of appearance, change of quantity, damaged tablets/capsules, presence of foreign matters.
  - Any defect of containers and external package, e.g., change of the surface, container leakage, broken syringe/piston, missing components, fault of apparatus.
  - Any breach in the label, e.g., missing or illegible label.
  - Any falsification of the drug or apparatus, e.g., a confusion of drug, its falsification or substitution is suspected.
- Transportation complaints are the claims associated with transportation of drugs and include damage of shipping carton box, damage of secondary package during receipt of goods, missing drug in the package, unsuitable transportation conditions.

Process

If any of the above quality complaints is found or received, the filled out quality complaint report form should be sent to the Sponsor (clinical trial manager) within 24 hours. Local monitor of the corresponding trial must be informed concurrently about the complaint. If possible, a picture of damaged material must be attached to the report. The suffered/damaged material must be retained and kept safe in accordance with the storage conditions indicated on the label and/or returned to the Sponsor upon Sponsor's request.

16.2 Appendix 2. TSS (Tonsillopharyngitis Severity Score) questionnaire

TE_004_ANG_LOZ	TONSILLOPHARYNGITIS SEVERITY SCORE (TSS)	PATIENT _____

Visit*	Evaluation point	Discomfort severity*	SORE THROAT	DIFFICULTY IN SWALLOWING	SALIVATION	PHARYNGEAL MUCOSA HYPEREMIA	BODY TEMPERATURE INCREASE**
VISIT 1	**BASELINE**	no symptom					
		insignificant symptom					
		moderate symptom					
		significant symptom					
VISIT 2	AFTER 3 DAYS OF THERAPY *evaluation before the first intake of the study drug on Day 4*	no symptom					
		insignificant symptom					
		moderate symptom					
		significant symptom					
VISIT 2/3	DISEASE OUTCOME*	no symptom					
		insignificant symptom					
		moderate symptom					
		significant symptom					

* To be filled in by the investigator at a Visit. Disease outcome applicable if TSS>2 after 3 days of therapy

Answers rate in points
0 = no symptom;
1 = insignificant symptom;
2 = moderate symptom;
3 = significant symptom.

** The axillary body temperature increase is rated as follows:
0 = <37.5 °C
1 = 37.5 to <38.5 °C
2 = 38.5 to <39.5 °C
3 = ≥ 39.5 °C

Investigator (Full name/Signature) _____/_____ Date _____

Version 1.0 of September 2, 2016 in Russian, compiled based on the final version of November 21, 2005 in German.
® AodSUgg. AC

16.3 Appendix 3. The patient's diary

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

PATIENT COUNSELING INFORMATION

DEAR PATIENT,

This is a patient's diary. Please read the instructions for filling-in carefully. In case of any questions, feel free to ask the Investigator.

You are participating in a clinical trial of efficacy and safety of Angal, lozenges with a menthol taste, compared to ANTI-ANGIN® FORMULA, a similar drug by action and composition, for therapy of acute, uncomplicated throat conditions.

The Investigator, based on your complaints and objective examination, has revealed that you have an acute, uncomplicated, infectious and inflammatory disease of the throat. One of the study drugs is prescribed to you to treat your condition: Angal, lozenges with a menthol taste, or ANTI-ANGIN® FORMULA, lozenges. Both you and the Investigator know which drug you are taking because this is an open (unblinded) trial. The information you are going to note in this diary is very important for this trial; therefore, please enter the data without corrections.

Fill in the patient's diary every day. Encircle the answers YES or NO according to your opinion: YES. Take the diary with you when you visit the trial site. You will enter the following data:

1. **Study drug use**: every time when you take a lozenge, record the time and briefly describe your complaints at that moment. Specify if you had a pain in your throat before the lozenge intake or not.
2. **Measurement of body temperature**: measure your body temperature 3 times a day or more frequently if needed. Specify a time and result of the measurement.
3. **Course of the disease**: specify if you noted any changes based on your subjective evaluation of the disease signs for which you take the lozenges.

If you feel worsening of state, increase of body temperature, aggravation of pain in your throat, contact the Investigator by phone _____!
If required, the Investigator may invite you for an unscheduled visit to the trial site for additional examination and therapy correction.

PRESCRIBING INFORMATION FOR THE STUDY DRUGS

Angal: 1 lozenge (slowly disintegrating in the mouth), use with at least a 2-hour intervals. Not more than 6–10 lozenges per day, therapy duration is up to 4 days.

Anti-Angin® Formula: 1 lozenge (slowly disintegrating in the mouth), use with at least a 2-hour interval. Maximum 6 lozenges per day, therapy duration is up to 5 days.

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

DAY 1: DD/MM/YYYY

1. USE OF THE STUDY DRUG: ANGAL/ANTI-ANGIN® FORMULA

1 lozenge/No. of administration	Specify the time of administration	Did you experience a pain in your throat during the use of lozenges?	Complaints/Notes
1	HH:MM	YES / NO	
2	HH:MM	YES / NO	
3	HH:MM	YES / NO	
4	HH:MM	YES / NO	
5	HH:MM	YES / NO	
6	HH:MM	YES / NO	
7	HH:MM	YES / NO	
8	HH:MM	YES / NO	
0	HH:MM	YES / NO	
10	HH:MM	YES / NO	

2. BODY TEMPERATURE

	Specify the time of measurement	RESULT OF MEASUREMENT
MORNING	HH:MM	_____°C
DAY	HH:MM	_____°C
EVENING	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C

3. COURSE OF THE DISEASE

	Specify the evaluation time	Based on your subjective evaluation of the disease symptoms, can you say that you have improved so much that you do not need to use the lozenges anymore?
MORNING	HH:MM	YES / NO
DAY	HH:MM	YES / NO
EVENING	HH:MM	YES / NO

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

DAY 2: DD/MM/YYYY

1. USE OF THE STUDY DRUG: ANGAL/ANTI-ANGIN® FORMULA

1 lozenge/No. of administration	Specify the time of administration	Did you experience a pain in your throat during the use of lozenges?	Complaints/Notes
1	HH:MM	YES / NO	
2	HH:MM	YES / NO	
3	HH:MM	YES / NO	
4	HH:MM	YES / NO	
5	HH:MM	YES / NO	
6	HH:MM	YES / NO	
7	HH:MM	YES / NO	
8	HH:MM	YES / NO	
0	HH:MM	YES / NO	
10	HH:MM	YES / NO	

2. BODY TEMPERATURE

	Specify the time of measurement	RESULT OF MEASUREMENT
MORNING	HH:MM	_____°C
DAY	HH:MM	_____°C
EVENING	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C

3. COURSE OF THE DISEASE

	Specify the evaluation time	Based on your subjective evaluation of the disease symptoms, can you say that you have improved so much that you do not need to use the lozenges anymore?
MORNING	HH:MM	YES / NO
DAY	HH:MM	YES / NO
EVENING	HH:MM	YES / NO

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

DAY 3: DD/MM/YYYY

1. USE OF THE STUDY DRUG: ANGAL/ANTI-ANGIN® FORMULA

1 lozenge/No. of administration	Specify the time of administration	Did you experience a pain in your throat during the use of lozenges?	Complaints/Notes
1	HH:MM	YES / NO	
2	HH:MM	YES / NO	
3	HH:MM	YES / NO	
4	HH:MM	YES / NO	
5	HH:MM	YES / NO	
6	HH:MM	YES / NO	
7	HH:MM	YES / NO	
8	HH:MM	YES / NO	
0	HH:MM	YES / NO	
10	HH:MM	YES / NO	

2. BODY TEMPERATURE

	Specify the time of measurement	RESULT OF MEASUREMENT
MORNING	HH:MM	_____°C
DAY	HH:MM	_____°C
EVENING	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C

3. COURSE OF THE DISEASE

	Specify the evaluation time	Based on your subjective evaluation of the disease symptoms, can you say that you have improved so much that you do not need to use the lozenges anymore?
MORNING	HH:MM	YES / NO
DAY	HH:MM	YES / NO
EVENING	HH:MM	YES / NO

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

DAY 4: DD/MM/YYYY

1. USE OF THE STUDY DRUG: ANGAL/ANTI-ANGIN® FORMULA

1 lozenge/No. of administration	Specify the time of administration	Did you experience a pain in your throat during the use of lozenges?	Complaints/Notes
1	HH:MM	YES / NO	
2	HH:MM	YES / NO	
3	HH:MM	YES / NO	
4	HH:MM	YES / NO	
5	HH:MM	YES / NO	
6	HH:MM	YES / NO	
7	HH:MM	YES / NO	
8	HH:MM	YES / NO	
0	HH:MM	YES / NO	
10	HH:MM	YES / NO	

2. BODY TEMPERATURE

	Specify the time of measurement	RESULT OF MEASUREMENT
MORNING	HH:MM	_____°C
DAY	HH:MM	_____°C
EVENING	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C

3. COURSE OF THE DISEASE

	Specify the evaluation time	Based on your subjective evaluation of the disease symptoms, can you say that you have improved so much that you do not need to use the lozenges anymore?
MORNING	HH:MM	YES / NO
DAY	HH:MM	YES / NO
EVENING	HH:MM	YES / NO

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

DAY 5: DD/MM/YYYY

1. USE OF THE STUDY DRUG: ANGAL/ANTI-ANGIN® FORMULA

1 lozenge/No. of administration	Specify the time of administration	Did you experience a pain in your throat during the use of lozenges?	Complaints/Notes
1	HH:MM	YES / NO	
2	HH:MM	YES / NO	
3	HH:MM	YES / NO	
4	HH:MM	YES / NO	
5	HH:MM	YES / NO	
6	HH:MM	YES / NO	
7	HH:MM	YES / NO	
8	HH:MM	YES / NO	
0	HH:MM	YES / NO	
10	HH:MM	YES / NO	

2. BODY TEMPERATURE

	Specify the time of measurement	RESULT OF MEASUREMENT
MORNING	HH:MM	_____°C
DAY	HH:MM	_____°C
EVENING	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C
Additionally	HH:MM	_____°C

3. COURSE OF THE DISEASE

	Specify the evaluation time	Based on your subjective evaluation of the disease symptoms, can you say that you have improved so much that you do not need to use the lozenges anymore?
MORNING	HH:MM	YES / NO
DAY	HH:MM	YES / NO
EVENING	HH:MM	YES / NO

TE_004_ANG_LOZ	THE PATIENT'S DIARY	PATIENT _____

The patient was instructed on the diary completion rules. The diary was given to the patient on Day 1 visit.

Investigator (Full name/Signature) _____/_____ Date_____

The diary was returned by the patient on time, according to the protocol. The data were entered correctly, all the corrections (if any) were discussed with the patient.

Investigator (Full name/Signature) _____/ _____ Date_____

16.4 Appendix 4. A visual analogue scale for sore throat evaluation

TE_004_ANG_LOZ	THE VAS (VISUAL ANALOGUE SCALE) FOR SORE THROAT EVALUATION	PATIENT No. _____

VISIT: ☐ 1
☐ 2
☐ 3
☐ unscheduled

Date:

		/			/				
D	D		M	M		Y	Y	Y	Y

Time:

		:		
H	H		M	M

Instructions for the patient: *please evaluate the severity of pain in your throat according to a scale of 0 (no pain) to 100 (the worst pain one can ever imagine) and draw a vertical line so that it crossed the scale below at the point corresponding to the pain in your throat at the present moment.*

No pain _____ The worst pain one
0 100 can ever imagine

Investigator

(Full name/Signature)_____/_____

Version 1.0 of September 12, 2016 in Russian