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Comparison of Tonsilgon N and local herbal anti-inflammatory medicine in patients with tonsillitis

Submission date 12/05/2021	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 25/05/2021	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 05/09/2022	**Condition category** Respiratory	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Tonsillitis is an infection of the tonsils at the back of your throat. It is a common childhood illness, but teenagers and adults can get it too.
There is little information about the influence of Tonsilgon N on local immunity and data about the mechanism of action. It is estimated that valuable data about Tonsilgon N action on immune cell level will be received during this study.
The efficacy of Tonsilgon N treatment will be compared to the treatment with Sage lozenges Natur Produkt.
Objective No.1 - to evaluate the influence of Tonsilgon N on local immunity parameters of the throat;
Objective No 2 - to evaluate the clinical efficacy of Tonsilgon N treatment compared to another standard herbal drug (Sage lozenge);
Objective No. 3 - to evaluate frequency, seriousness, and expectedness of Adverse Events and SUSARs between the study groups.

Who can participate?
Adults aged 18 - 55 years, suffering from tonsilitis.

What does the study involve?
All subjects were consulted by the ENT-specialist and fully examined including local immunity status evaluation. Participants were randomly allocated to receive Tonsilgon N treatment or Sage lozenges Natur Produkt for 37 days. All included subjects visited the site four times over 37 days.

What are the possible benefits and risks of participating?
Possible benefits of participating were:
1. All subjects were provided with Investigational Products for the whole study.
2. All subjects were fully examined by ENT-specialist (pharyngoscopy, consulting, cell blood count).
3. Local immunity status of oral cavity was evaluated and results were discussed with the

Subjects.
4. Based on collected experience, use of study product Tonsilgon N and comparator product Shalfej, orodispersible tablet (“Valeant” LLC), is effective for treatment of upper respiratory tract disease (tonsillitis, pharyngitis, laryngitis), that present as more rapid resolution of respective symptoms caused by local anti-inflammatory and antiseptic effects.

The possible risk was related to AEs developing and some study procedures:
1. Blood sample collection for blood count may be associated with discomfort for patients, related to pain during injection, and possible bruising in venipuncture points. Significantly rarer in venipuncture spot infectious complication or systemic infection may develop. Vertigo and/or weakness may be observed during and soon after blood sample collection.
2. During pharyngoscopy patient may experience pressure at the base of the tongue and mild discomfort, during scarification sample collection from the surface of tonsils and throat – mild pain and dry heaving. Moreover, mechanical damage to oropharyngeal mucosa (scarification sample collection for local immunity assessment) and tonsil during inflammation may promote secondary bacterial infection and complicated presentation of tonsillopharyngitis.
3. Other study procedures, conducted in present protocol, including physical examination, are routine for general clinical practice. Frequency of those procedures does not create any discomfort for patient.
4. AEs related to Tonsilgon are GI tract related AEs (nausea, vomiting) and allergic reactions. Use of comparator product Shalfej, orodispersible tablet (“Valeant” LLC) may also lead to allergic reactions.

Where is the study run from?
Federal State Budgetary Institution Policlinic #3 of Administrative Directorate of the President of the Russian Federation (Russia)

When is the study starting and how long is it expected to run for?
November 2019 to December 2020

Who is funding the study?
Bionorica SE (Germany)

Who is the main contact?
Kirill Bessonov, kirbess@gmail.com

Contact information

Type(s)
Public

Contact name
Dr Elena Savlevich

ORCID ID
http://orcid.org/0000-0003-4031-308X

Contact details
19 building 1A
Marshala Timoshenko Str.
Moscow

Russian Federation
121359
+7 (499) 149-58-27
savllena@gmail.com

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Nil known

Study information

Scientific Title
Evaluation of anti-inflammatory properties of herbal medicines in patients with tonsillopharyngitis – interventional, open, randomized, one center comparative trial in parallel groups.

Study objectives
Whether Tonsilgon N can effectively influence main local immunity pa-rameters and what parameters are most changeable. Whether Tonsilgon N is more effective compare to local herbal anti-inflammatory remedy against tonsillitis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/12/2019, Ethics Committee at Federal State Budgetary Institution Policlinic #3 of Administrative Directorate of the President of the Russian Federation (31 Grokholsky lane, Moscow 129090; +7 495 9826571; anikin_gs@pudb.ru), ref: 1-12-2019

Study design
Monocentric randomized controlled open-label parallel-group

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
See additional file (in Russian) ISRCTN80067058_PIS_Russian_v1_25Aug2019 (added 01/06/2021)

Health condition(s) or problem(s) studied
Treatment of acute tonsillo-pharyngitis or exacerbation of chronic tonsillopharyngitis and evaluation of local immunity parameters in adults

Interventions
Study Treatments: Tonsilgon N arm - Tonsilgon N 25 drops every 2 hrs for the first 3 days of treatment then 25 drops TID till day 7.

Herbal lozenges arm – 1 pastil every 2 hrs for the first 3 days of treatment than 1 pastil TID till day 7.

Study evaluations: Scarification sample collection of upper mucosa layer of tonsils and back pharynx, Pharyngoscopy, Blood count, Vital signs.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tonsilgon N (drops, Bionorica SE), Sage lozenges (Natur Produkt)

Primary outcome measure
1. Tonsillopharyngitis severity: TSS (Tonsillopharyngitis Severity Score) score at day 0 and day 4
TSS scale version of contract research organization Appletree AG was adapted for purposes of current study.
TSS is a questionnaire for evaluation of presence and severity of following symptoms: throat pain, difficulty to swallow, salivation, pharynx mucosa hyperemia, hyperthermia by 4-point scale.

Secondary outcome measures
1. Proportion of patients achieved clinically significant improvement (TSS score ≤ 5) at study day 4
2. Severity of pain or discomfort in throat by TSS subscale – proportion of patients with every grade of severity at baseline and day 4
3. Time until complete resolution of every symptom evaluated by patients' diary
4. Proportion (%) of patients completely recovered by day 4 (disease outcome by objective evaluation of Study Doctor)
5. Dynamic of every tonsillopharyngitis symptom severity by 4-point scale (0 to 3) at visit 2 compared to visit 1
6. Dynamic of every tonsillopharyngitis symptom severity by 4-point scale (0 to 3) at visit 3 compared to visit 1
7. Dynamic of local immunity markers (SIgA, TNF, IFN-α, lysozyme, lactoferrin, IL-1, -6, -8, -10, and-17) in mucosa of tonsils and back pharynx at visit 2 compared to visit 1
8. Dynamic of local immunity markers (SIgA, TNF, IFN-α, lysozyme, lactoferrin, IL-1, -6, -8, -10, and-

17) in mucosa of tonsils and back pharynx at visit 3 compared to visit 1
9. Dynamic of local immunity markers (SIgA, TNF, IFN-α, lysozyme, lactoferrin, IL-1, -6, -8, -10, and-17) in mucosa of tonsils and back pharynx at visit 4 compared to visit 1
10. Proportion of patients (%), in which contents of local immunity markers (SIgA, TNF, IFN-α, lysozyme, lactoferrin, IL-1, -6, -8, -10, and-17) in mucosa of tonsils and back pharynx at visit 2 was equivalent to values in healthy persons (if deviation was detected at visit 1)
11. Proportion of patients (%), in which contents of local immunity markers (SIgA, TNF, IFN-α, lysozyme, lactoferrin, IL-1, -6, -8, -10, and-17) in mucosa of tonsils and back pharynx at visit 3 was equivalent to values in healthy persons (if deviation was detected at visit 1)
12. Proportion of patients (%), in which contents of local immunity markers (SIgA, TNF, IFN-α, lysozyme, lactoferrin, IL-1, -6, -8, -10, and-17) in mucosa of tonsils and back pharynx at visit 4 was equivalent to values in healthy persons (if deviation was detected at visit 1)

Overall study start date
01/11/2019

Completion date
31/12/2020

Eligibility

Key inclusion criteria
1. Males and females aged 18 to 55 (inclusive)
2. Diagnosis at inclusion – “mild acute tonsillopharyngitis” or “chronic tonsillopharyngitis exacerbation”
3. Body temperature measured in armpit ≤ 37.5°C
4. Tonsillopharyngitis severity by TSS ≥ 8 points
5. Time from first symptoms’ onset until visit to physician – not more than 24 hours
6. Signed informed consent form
7. For females with childbearing potential and males – consent to use effective method of contraception across all study and following 1 month after its completion

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
60 subjects

Total final enrolment
70

Key exclusion criteria

1. Any signs and symptoms of bacterial (streptococcal) tonsillopharyngitis (McIsaac scale score > 1)
2. Positive result of express-test Streptatest
3. Consumption of antibiotics during < 48 hours prior to inclusion
4. Patients earlier received tonsillectomy or tonsillotomy
5. Use of local treatments for oropharyngeal disease (aerosols, gargle solutions, tablets /orodispersible tablets/lozenges) during 24 hours prior to inclusion and/or impossibility to discontinue use of any local treatments, except used in study, during study course
6. Use of systemic, inhaled or nasal glucocorticosteroids during 30 days prior to study start, injectable corticosteroids – during 3 months prior to study start and/or plans to use glucocorticosteroids (except topical dermal ones) during the course of study
7. Impossibility to withdraw for study period any medicinal preparations that could influence result of current study, e.g., antiviral medicines, or preparations incompatible with study treatments (see Section "Prohibited concomitant therapies")
8. Pharyngitis granulosa
9. Signs of fungal oropharyngeal infection (white caseous plaques easy removable by pallet)
10. Clinical signs of diphtheria
11. Presence of signs of sinusitis, otitis, eustachitis, laryngitis, tracheitis, bronchitis (since indicated conditions could demand indication of medicines, that could possibly affect evaluation of study results; it is acceptable to include patients with rhinitis with use of therapies permitted by the Protocol)
12. Vaccination of patient conducted in 30 days prior to inclusion
13. Assumed low patients' compliance with treatment or inability to undergo procedures and follow restrictions according to study protocol (e.g., as a result of psychiatric disorders)
14. Clinically meaningful deviations of blood count, including any of the following signs: leukocytosis > 9x10^9/L, neutrophilia >78%, band neutrophil content >6% or presence of younger neutrophil forms, erythrocyte sedimentation rate >30 mm/h
15. Liver diseases
16. History of craniocerebral injury
17. Brain diseases
18. Any cardiovascular, kidney, liver, gastrointestinal (GI), endocrine, and nervous system diseases or any other diseases/conditions that, by Study Doctor's opinion, could lead to unsafety of patients participation in the study
19. Any concomitant diseases that require use of medications influencing immune system (immune system modulators, stimulators, suppressors) or antibiotics
20. Need to use medications that act through γ-aminobutyric acid receptors (e.g., barbiturates and benzodiazepines)
21. Pregnant, lactating women or women planning pregnancy during next two months;
22. Women of reproductive age, that did not confirm use of highly effective contraception methods (combined oral contraceptives, double barrier method)
23. Misuse of alcohol, or use of other psychoactive substances
24. Known hypersensitivity for any component of Tonsilgon N (chamomile, althea, oak bark, taraxacum, horsetail, walnut, milfoil, plants of Compositae family) or salvia and other related herbs (Asteraceae family)

Date of first enrolment

01/01/2020

Date of final enrolment

23/12/2020

Locations

Countries of recruitment
Russian Federation

Study participating centre
Federal State Budgetary Institution Policlinic #3 of Administrative Directorate of the President of the Russian Federation
31 Grokholsky lane
Moscow
Russian Federation
129090

Sponsor information

Organisation
Central State Medical Academy

Sponsor details
19 building 1A
Marshala Timoshenko Str.
Moscow
Russian Federation
121359
+7 499 140 1876
org@cgma.su

Sponsor type
Research organisation

Website
http://www.cgma.su/

ROR
https://ror.org/00xx5qr89

Funder(s)

Funder type
Industry

Funder Name

Results and Publications

Publication and dissemination plan
The results of this study will be published in some specialized non-russian journal.

Intention to publish date
01/12/2022

Individual participant data (IPD) sharing plan
The IPD are not expected to be shared.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1	25/08/2019	01/06/2021	No	Yes
Protocol file	version v2.0	11/09/2019	01/06/2021	No	No