# 1 TITLE PAGE

# Clinical Trial Protocol

Title:

A Protocol of a Multicenter, Randomized, Open-Label, Comparative Study of Therapeutic Efficacy, Safety and Tolerability of Imupret application in the therapeutic concept of delayed prescription of antibiotics in children, aged 6-12 with severe acute tonsillitis.

| | |
|---|---|
| Trial code: | ATi-2 |
| Working Title: | Imupret in tonsillitis |
| Clinical phase: | IV |
| Name of the investigational product: | Imupret® |
| Coordinating Investigator: | Prof. Dr. Vasyl Ivanovych Popovych |
| Sponsor: | Ivano-Frankivsk National Medical University<br>Prof. Dr. Vasyl Popovych<br>2, Galytska str.,<br>Ivano-Frankivsk,<br>Ukraine, 76000 |
| Version Number: | 1 February 2019 |
| Version Date: | 1.0 |

# SIGNATURE PAGE I

The signatory agrees to comply in all respects with this clinical trial protocol, the standards of Good Clinical Practice as defined in the "Note of Guidance on Good Clinical Practice (CPMP/ICH/135/95)" and related Guidelines and with all applicable regulatory requirements including national drug law and data protection law.

Coordinating Investigator

| Date (dd/mmm/yyyy) | Signature |
|---|---|
| | |

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# 3 ADMINISTRATIVE STRUCTURE

| | |
|---|---|
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# 4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse Event |
| AR | Adverse reaction |
| BDRM | Blind Data Review Meeting |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CTM | Clinical trial manager |
| ENT | Ear-nose-throat |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FAS | Full analysis set |
| FPI | First Patient In |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| ICD | International Classification of Diseases |
| ICH | International Committee of Harmonization |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| Int. | International |
| LPO | Last Patient Out |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSAID | Non-steroidal inflammatory drugs |
| PPS | Per protocol set |
| SAE | Serious Adverse Event |
| SAP | Statistical analysis plan |
| SE | Societas Europaea |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| V | Visit |
| VAS | Visual analogue scale |

# 5 TRIAL SYNOPSIS

| | |
|---|---|
| Trial code | ATi-2 |
| Title of Trial | A Protocol of a Multicenter, Randomized, Open-Label, Comparative Study of Therapeutic Efficacy, Safety and Tolerability of Imupret application in the therapeutic concept of delayed prescription of antibiotics in children, aged 6-12 with severe acute tonsillitis. |
| Working title | Imupret in tonsillitis |
| Trial Design | open-label, exploratory, comparative, multicentre, randomized, prospective, parallel-group study. |
| Clinical phase | IV |
| Inclusion diagnosis | Acute tonsillitis |
| Trial objectives | Assessment of the influence of Imupret (drops) prescriptions in the therapeutic concept of delayed prescription of antibiotics to:<br>• need for antibiotics<br>• regression of the tonsillitis symptoms<br>• duration of antipyretics administration |
| Number of patients | approximately N=200 (1:1 ratio active treatment: reference) |
| Specialization of investigator | Head of Department of Otorhinolaryngology<br>Head & Neck Surgery |
| Time schedule | Planned FPI (First patient in): approximately February 2019<br>Planned LPO (Last patient out): approximately December 2019 |
| Efficacy endpoints | **The main criterion (main variable):**<br>- - decrease in the severity of each symptom (complaint) that is part of the McIsaac scale of tonsillitis manifestations, up to 1 point or less. This variable is dichotomous, with the categories "treatment effective" and "treatment not effective":<br>- Treatment is effective - reducing the severity of each symptom (complaint) that is part of the Local Tonsillitis Manifestation Scale (0-15),of tonsillitis manifestations, up to 1 point or less in the evaluation stages. Absence of indications for prescribing antibacterial therapy<br>- Treatment is not effective - the condition given for the category "therapy is effective" is not met. |
| Secondary end-points | **Secondary variables:**<br>- a decrease in the severity of the symptoms of the underlying disease, at the 2- nd, 3 -rd and 4- th visits compared to the 1- st visit.<br>- decrease in the total score (the sum of scores for each symptom) according to the scale of local manifestations of tonsillitis at the 2-nd, 3-rd and 4-th visits in comparison with the 1-st visit.<br>- a decrease in temperature in the armpit at the 2-nd and 3-rd visits compared to the 1-st visit.<br>- a patient's self-assessment of the quality of life (every day).<br>- Duration of NSAID administration.<br>-Therapy compliance |
| Safety evaluation | - Adverse events (AEs), serious adverse events (SAEs)<br>- Incidence of adverse drug reactions (ADRs) |

<table>
<tr><td></td><td>- Overall assessment of tolerability</td></tr>
<tr><td>Methodology</td><td>
1. Medical history, demographic and anthropometric data at screening.<br>
2. Complaints, patient questioning by organs and systems – at each visit, including any unscheduled visit and telephone contact.<br><br>
All complaints are assessed using a 4-point rating scale, beginning from the visit at which the complaint was identified for the first time.<br><br>
3. Physical examination:<br>
skin and visible mucosa examination, palpation of abdomen and lymph nodes, oropharyngoscopy are performed at each visit including any unscheduled visit.<br><br>
Symptoms are assessed using a 4-point rating scale, beginning from the visit at which the symptom was identified for the first time.<br><br>
4. Evaluation of probability of acute bacterial tonsillitis in accordance to McIsaac scale (sum of scores)<br><br>
<table>
<tr><th>McIsaac scale (sum of scores)</th><th>The probability of the identification of β-hemolytic streptococcus in a smear from pharynx</th></tr>
<tr><td>-1 or 0</td><td>1%</td></tr>
<tr><td>1</td><td>10%</td></tr>
<tr><td>2</td><td>~17%</td></tr>
<tr><td>3</td><td>~35%</td></tr>
<tr><td>4 or 5</td><td>~50%</td></tr>
</table>
<br>
5. Complaints included in the Local Tonsillitis Manifestations Scale are assessed at each visit including any unscheduled visits<br><br>
6. Symptoms included in the Local Tonsillitis Manifestations Scale are assessed at each visit<br><br>
7. Axillary temperature assessment at each visit including any unscheduled visits.<br><br>
8. Clinical blood count, urinalysis and blood chemistry according to the investigator’s decision.<br><br>
9. Self-assessment of the patient’s state of health by him/herself and (or) his/her parents using a visual analogue scale is performed on a daily basis.
</td></tr>
</table>

| | |
|---|---|
| Inclusion criteria | 1. Children (males/females), 6 - 12 years old, with severe acute tonsillitis.<br>2. Possibility to initiate therapy within 72 hours since the onset of the disease symptoms.<br>3. Score 4-5 according to McIsaac Scale.<br>4. Patient's and (or) one of his/her parents' willingness and ability to fulfil the requirements of the Study Protocol.<br>5. Signed informed consent of the patient and (or) his/her parents for participation in the study. |
| Exclusion criteria | 1. Score -1 to 3 according to McIsaac Scale.<br>2. Indication for hospitalization, including:<br>3. purulent complications (peritonsillar abscess and others);<br>4. severe general condition.<br>5. Indication for immediate initiation of systemic antibiotic therapy<br>6. patients at risk of developing severe complications, including e.g. clinically relevant concomitant diseases of heart, lungs, kidneys, liver, neuromuscular apparatus, cancer diseases, immunosuppression, diabetes mellitus, cystic fibrosis.<br>7. suspected infectious mononucleosis (by clinical signs);<br>8. use of systemic antibacterial or antifungal agents, systemic glucocorticosteroids, cytostatics, immunomodulatory drugs, "interferons" or interferon derivatives during the last 14 days prior to inclusion;<br>9. presence of haemorrhagic or pronounced necrotic process in oral cavity or pharynx, including the lymphoid ring.<br>10. Intolerability or individual hypersensitivity to any of the study drug ingredients and the reference treatment scheme. |
| Sample size calculation | **Justification of the number of subjects**<br>This trial is parallel, two-group, with the same size groups.<br>The planned test power is 80% (the probability of making a second kind error is 0.2), the two-way probability of making a type 1 error is 0.05. The sample size was estimated by the main variable of the clinical trial.<br>Thus, this trial was a comparative for superior efficiency.<br>When proving superior therapeutic efficacy, the following statistical hypotheses are tested:<br>H0: e £ d versus On: e> d, where d is the limit of greater efficiency — the marginal value of clinically important differences, at which it can be considered that the tested drug exceeds its effectiveness by control (in this study it was taken equal to 15%); e - estimated (observed) differences between groups in therapeutic efficacy.<br>Given that the main variable is dichotomous, the size of each group can be estimated using the following expressions:<br>n control = k · n main<br>$$n_{main} = \frac{(z_\alpha + z_\beta)^2}{(\varepsilon - \delta)^2} \cdot \left[ \frac{p_{Control} \cdot (1 - p_{Control})}{k} + p_{main} \cdot (1 - p_{main}) \right]$$<br>where: $z_\alpha$ and $z_\beta$ —the corresponding percentage points of the standard normal distribution; d - the minimum acceptable value of clinically important differences; e - presumed (observable) differences between groups on therapeutic efficacy (the difference between the shares of positive results in groups); pcontrol and p main —shares of positive results in the |

main and control groups, respectively; k - coefficient for unequal number of patients in groups (control is greater than the main); nmain и ncontrol - the planned number of patients in the main and control groups, respectively; α is the boundary value of the error of the 1st kind (level of significance); β - is the boundary value of the error of the second kind.

In the planned study, it was assumed that the number of patients in the main and control groups was the same (k = 1), the significance level was α = 0.05 (two-sided); the boundary value of the error of the second kind is β = 0.2 (which makes it possible to achieve a research power of 80%). Baseline data and the results of calculations using the above formula are given in Table. 1.

**Table 1 - Baseline and Sample Size Estimation Results**

| Statistical indicator | Value of the indicator |
|---|---|
| Multiplicity factor k | 1 |
| Boundary probability error of the first kind α | 0,025 |
| The probability of an error of the second kind β | 0,2 |
| The percentage point S.N.R. for α | 1,96 |
| The percentage point S.N.R. for β | 0,84 |
| The observed frequency of the positive effect for the control group pcontrol | 0,75 |
| Estimated value of the positive effect for the main group pmain | 0,90 |
| The value of the clinically important differences d | 0,15 |
| Estimated differences between groups e | 0,0 |
| The size of the main group nmain | 97 |
| The size of the control group ncontrol | 97 |
| Estimated share of departures | 3 |
| Adjusted main group size | **100** |
| Adjusted control group size | **100** |

***The final number of patients in each group was adjusted for their possible dropout. Thus, the final number of subjects in each group was 100 patients (200 patients in total).***

| | | |
|---|---|---|
| Test treatment | - Treatment with Imupret® oral drops according to the respective Summary of Product characteristics<br>(Imupret® coated tablets or oral drops during acute period for 5 days, afterwards switch to the subacute dosage regimen for further 28 days<br>- Sparing diet; fractional feeding (5-6 times a day) in small portions with the exception of coarse, spicy, heavily digestible foods<br>- Elimination of factors irritating pharyngeal mucosa (thermal, chemical)<br>- As needed, Paracetamol (Acetaminifen) in a single dose of up to 400 mg not more than 3 times daily or paracetamol in a single dose of up to 500 mg 3-4 times daily (if necessary).<br>- Topical agents such as Benzydamine, Lidocaine as needed (in case of severe sore throat). | |
| Reference treatment | - Sparing diet; fractional feeding (5-6 times a day) in small portions with the exception of coarse, spicy, heavily digestible foods<br>- Elimination of factors irritating pharyngeal mucosa (thermal, chemical)<br>- As needed, Paracetamol (Acetaminifen) in a single dose of up to 400 mg not more than 3 times daily or paracetamol in a single dose of up to 500 mg 3-4 times daily (if necessary).<br>- Topical agents such as Benzydamine, Lidocaine as needed (in case of severe sore throat). | |
| Investigational Medicinal Product | Active (add on) treatment | Imupret® oral drops |
| | Mode of administration and dosage regimen | Imupret® oral drops<br>*Dosage for acute symptoms:*<br>Children from 6 to 12 years: 15 drops 5-6 times daily<br>Adults and adolescents from the age of 12 years:<br>25 drops 5-6 times daily<br>*Dosage after acute symptoms have subsided:*<br>Children from 6 to 12 years: 15 drops 3 times daily<br>Adults and adolescents from the age of 12 years:<br>25 drops 3 times daily |
| Duration of treatment | Disease will be evaluated 36-48 hours prior to active treatment.<br><br>Active Imupret® treatment group: 10 treatment days<br>Reference treatment group: 10 days<br><br>Afterwards, there will be a follow up observation phase of 1 months | |

## SCHEDULE OF ASSESSMENTS

| V1 | | V2 | | V3 (*Telephone call)* | | | | | V4 | V5 |
|---|---|---|---|---|---|---|---|---|---|---|
| day 1 | day 2 | day 3 | day 4 | day 5 | day 6 | day 7 | day 8 | day 9 | day 10 | day 28 |

*Study group 1*

| Imupret (dosage acute phase) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Reference treatment | | | | | | | | | | |

*Study group 2*

| Reference treatment | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|

| | | |
|---|---|---|
| V1 | day 1 | Screening, randomization, prescription of treatment |
| V2 | day 3 | Status evaluation, possible prescription of antibiotics |
| V3 | day 5 ±1 | Evaluation of treatment efficacy, telephone call |
| V4 | day 10 ±1 | Evaluation of treatment efficacy, end of reference treatment |
| V5 | day 28 | Telephone call |

# 6 INTRODUCTION

## 6.1 Medical background

The problem of acute inflammatory diseases of the tonsils is one of the most urgent in modern clinical medicine. The prevalence of pathology ranges from 2 to 15% of the total population. Morbidity is especially common among children: 50% of patients aged 5 to 15 years, often in early school age. The incidence among the age group 18 years and older is 11.36 cases per 1000 population per year, among children aged 0-17 years - 62.61. Such patients constitute a significant proportion of outpatients both among otorhinolaryngologists and pediatricians, and the diagnosis of inflammation of the lympho-pharyngeal apparatus is established in 19-20% of the cases among the 20 most commonly diagnosed diseases (in accordance to Medical Data Management).

Acute tonsillitis (ICD J03.0-J03.9) refers to viral or bacterial tonsillitis. Acute tonsillitis in most cases is due to viral infections. The most frequent pathogens are adenovirus, Epstein-Barr virus and enteroviruses, including Coxsackie viruses. Bacterial acute tonsillitis occurs in immunocompetent children in 20-30% of cases, adults - in 5-15%, and the most frequent cause of it is β-hemolytic streptococcus group A (GABS). Acute relapsing / recurrent tonsillitis (ICD J35.0) refers to repeated acute tonsillitis and is not a sign of bacterial tonsillitis.

Acute tonsillitis is defined as the sudden appearance of the following specific symptoms: sore throat, hyperemia, edema of the tonsils, increase in swollen lymph nodes (regional lymphoadenopathy) and nonspecific additional symptoms like fever, weakness and joint pain. It has to be noticed, that there are no pathognomonic symptoms of bacterial tonsillitis. To assess the patient's condition and to determine the indications for antibacterial therapy, the McIsaac scale is a commonly used tool for decision. This scale is used to classify patients according to their symptoms and to determine the patients for whom antibiotic therapy is not indicated.

| **McIsaac scale (sum of scores)** | The probability of the identification of β-hemolytic streptococcus in a smear from pharynx |
|---|---|
| -1 or 0 | 1% |
| 1 | 10% |
| 2 | ~17% |
| 3 | ~35% |
| 4 or 5 | ~50% |

Thus, in most cases of acute tonsillitis (even if there are 4-5 points according to the scale), it has to be taken into account that there is a low probability of the presence of GABS. Therefore, there are no unconditional indications for the prescription of antibiotics.

It should be noted that unjustified antibiotic therapy of acute tonsillitis is only based on the symptom "sore throat" or "exudate (plaque) tonsils" and plays a significant role in the formation of antibiotic resistance. Antibiotic therapy does not affect pain. In order to avoid the

irrational use of antibiotics, one should distinguish the desire of the patient or his parents to get rid of the pain, from the rational assessment of the doctor for all pros and cons about an antibacterial therapy.

To prevent unjustified prescription of antibiotics, a therapeutic concept of delayed administration is proposed. A patient with acute tonsillitis is prescribed treatment with antibacterial agents in a delayed manner (a prescription is written out, the dose and the frequency of administration is calculated). In the absence of positive effect within 36-48 hours from the beginning of treatment with Imupret the antibacterial therapy with antibiotics is started. The advantage of deferred antibiotic prescription is, that a higher number of patients and doctors, awaiting antibiotic therapy, may be more agreeable with this way of treatment than with a complete rejection of the antibiotics prescription. This is why delayed use of antibiotics is an important treatment strategy to reduce the number of unreasonable prescription of antibacterial agents.

Considering this fact, it becomes necessary to use drugs with a complex effect on the main processes of pathogenesis and have an evidence-based efficacy base for acute tonsillitis. At the present moment, there is an insignificant evidence base for the application of the phytoneering drug Imupret in acute tonsillitis. The spectrum of its pharmacological properties includes antiviral, antibacterial, antiinflammatory and immunomodulating effects. The combination of these properties makes it possible to influence practically all parts of acute tonsillitis. Additionally a good safety profile allows to consider Imupret as an adequate basic therapy for the treatment of acute tonsillitis, especially in the therapeutic concept of of delayed prescription of antibiotics. The already existing studies were not conducted under GCP conditions. Confirmation of the high effectiveness of Imupret in the treatment of acute tonsillitis would serve as a rationale for optimizing the treatment regimen of this nosology and recommendations for the inclusion of the drug in national guidelines.

## 6.2 Drug profile

### 6.2.1 Pharmacology / Safety profile

#### 6.2.1.1 Pharmacology

Herbal products containing individual drugs, similar to this herbal combination product, were developed several decades ago on the basis of traditional medical use. They have gained wide recognition and clinical application.

Pharmacodynamic *in vitro* and *in vivo* studies have demonstrated anti-inflammatory, antiviral and antibacterial, immune-modulatory properties of components of Imupret (please refer to 2.6.2 and 2.4) [Kommission E, 1984-1989 (1, 2, 3), 1990 (5, 6, 7), 1992 (8)].

The pharmacodynamic effects might be based on the more or less plant specific ingredients like flavonoids, polysaccharides, terpenoids, sesquiterpens etc. Pharmacokinetic data are not available to sufficiently show their systemic availability in humans. Effects of the single plants or of the extract from all plants contained in Imupret cannot clearly be linked to single plant specific ingredients. However, the effects of the complex extract have been investigated in in-vitro or in-vivo animal experiments. The results indicate that it displays the anti-inflammatory, antibacterial, antiviral, or immune-modulatory effects. This can also be measured after systemic application including oral and intraperitoneal administration. This indicates that the basic characteristics of the single herbal drugs known from administration according to the monographs are also displayed after systemic administration in the dosage and composition of Imupret (module 2.4).

It is generally accepted that the combination of drugs in a multi-component mixture may lead to increased or maintained efficacy while decreasing the dosage of the individual components to avoid toxicity. The mathematical basis of this concept was already set up in 1963 by Webb in a simplified model, the so-called 'fractional product method' [Webb, 1963 (9)].

#### 6.2.1.2 Safety profile

Imupret and its herbal constituents Althaeae radix, Millefolii herba, Taraxaci herba, Equiseti herba, Juglandis folium, Matricariae flos, and Quercus cortex have a long history of traditional use. Furthermore, Imupret (formerly Tonsilgon) has been prescribed by doctors over several decades. From these applications a very good safety profile is apparent.
The data from all clinical surveys provide just one category of ADRs that came up: gastrointestinal complaints (0.17 %) that eventually stopped the patients from further taking Imupret.
As been described in 2.5.4, all surveys were performed in private practices of general practitioners or ENT doctors. Patients of all age groups have been included. The medical conditions investigated covered recurrent infections of the upper airways, including tonsillitis, catarrhal rhinosinusitis and tracheobronchitis.
In total, the intake of Imupret coated tablets or oral drops was monitored for 2483 patients. Both solid and liquid application forms have been used, numbers of applications of each formulation in the 2 older surveys of Maier and Maier 1974 [9] and Sprenger 1975 [10] are unknown. The large majority of patients were treated either for 2 weeks ([Berger T. 2008 (11), Vavilova V. et al. 2016 (12)]) or 3 months.

Adverse events:
Of 2 adverse events with Imupret oral drops reported in 1 of 3 surveys, both were related to the gastro-intestinal system: vomiting and stomach ache. Both were transitory; dose-withdrawal was the consequence in both cases. No adverse event was reported with the coated tablets in this surveillance.

Post-marketing experience:
Although more than 653 million DDDs of Imupret®/Tonsilgon® oral drops and coated tablets were marketed from 1973 until now, only 7 spontaneous cases of serious adverse drug reactions (sADR) in association with Imupret®/Tonsilgon® oral drops or coated tablets have been reported worldwide. Hereof only two cases of sADR were assessed as possibly related to the intake of Imupret®/Tonsilgon® by the MAH, one case was assessed as unlikely due to evident other reason and four cases were assessed as unassessable because of insufficient and / or contradictory information.

## 6.3 Description and rationale for conducting the trial

At present, there is minor evidence of using the phytoneering-based drug product Imupret® in acute tonsillitis, pharyngitis and tonsillopharyngitis. The spectrum of its pharmacological properties includes antiviral, anti-inflammatory, and immunomodulatory action. The aggregate of these properties allows affecting almost all pathogenetic process links underlying the nosology in question, and favourable safety profile allows viewing Imupret as a basic therapeutic agent in treatment of non-bacterial forms of acute tonsillitis, pharyngitis, and tonsillopharyngitis. Our previous work showed that the use of Imupret in patients with non-bacterial tonsillitis accelerates regression of symptoms of tonsillitis and reduces the need for antibiotics. At the same time, there is a lack of studies, valid from the viewpoint of compliance with GCP standards have been conducted. Confirmation of high efficacy of Imupret in treatment of the above nosology group would be served as a justification for optimization of this nosology treatment scheme of delayed antibiotic prescription and recommendations for inclusion of this drug product into the national guidelines.

**In the context of this clinical trial the two questions that are to be answered are:**

1. Does Imupret®, taken during the diseases acute period help reduce the frequency of antibiotic use in children aged 6-12 ?
2. Does Imupret®, taken during the diseases acute period helps to accelerate the regression of symptoms in children aged 6-12?

3. Is the use of antibiotic delay technology safe for children aged 6-12 years?

## 6.4 Risk / benefit assessment

Imupret combines the anti-microbial, anti-inflammatory and immune-modulatory effects of seven herbal drugs used traditionally in the combination product Imupret. Clinical surveys have demonstrated that it can be successfully applied in therapy of acute infections and inflammations of the upper respiratory tract.

The benefit of therapy with Imupret N can be concluded from long years of successful application in medical practice and in self-medication, but also from the results of the post marketing surveillances and experience report. Side effects observed in clinical surveys are almost exclusively gastro-intestinal complaints or allergic skin reactions which lead to intake termination or dose adjustment.

## 6.5 Guidelines for the development of the trial protocol

The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki from 2013, the principles of GCP as described in the ICH E6 guideline and the provisions of the EU Directive 2001/20/EC on the implementation of GCP in the conduct of clinical trials. All aspects of these regulations were observed in the clinical trial development process.

# 7 TRIAL OBJECTIVES

The aims of this clinical trial are:

To investigate the influence of Imupret prescriptions in the therapeutic concept of delayed prescription of antibiotics to:

- To compare the need for antibiotics in patients, received Imupret in addition to conventional therapy and in patients of the control group (received conventional therapy only)
- To evaluate the effect of the study drug in complex with conventional therapy versus conventional therapy only on regression of the tonsillitis symptoms
- To evaluate the effect of the study drug in complex with conventional therapy versus conventional therapy only on duration of antipyretic (paracetamol as antipyretic) administration.

# 8 TRIAL PLAN

## 8.1 Trial design

This is an open-label, exploratory, comparative, multicenter, randomized, prospective, parallel-group phase IV clinical trial. The trial is designed in order to reveal effects of an additional Imupret therapy in comparison to the standard therapy alone (diet, NSAID, elimination of irritative factors, local anaestethics).

Imupret® oral solution is registered and marketed in the Ukraine. The dose of Imupret was selected based on the recommendations given in the respective Summary of Product Characteristics of both dosage forms, which is also reflected in the package leaflet, respectively.

## 8.2 Sample size estimation

The clinical trial is designed in order to obtain a valid description of the in vivo performance of the active (add-on) treatment of Imupret in comparison to the reference standard treatment alone. Endpoints are defined as exploratory endpoints. Depending of the data finally obtained, several exploratory descriptive and statistic evaluations will be performed, so that a biometrically based sample size estimation is not necessary. However, in order to guarantee a sufficient sample size for exploratory analyses of the data captured, a sample size of N=200 will be included. Treatments will be assorted in a 1:1 ratio, i.e. N=100 will receive an add-on treatment with Imupret® and N=100 will receive the standard treatment only.

## 8.3 Trial treatment

The IMPs in this trial are Imupret® oral drops. The preparation is registered and available on the Ukrainian market without prescription. Therefore, the formulation, manufacturing, packaging and labelling of the IMPs follow the principles of Good Manufacturing Practice and currently valid national Ukrainian requirements. The detailed description covering all aspects regarding quality and safety of Imupret® oral drops are part of the respective Summary of Product characteristics.

### 8.3.2 Imupret® oral solution

The composition of the medicinal product is as follows:

*Active substances:* 100 g drops contain 29 g of an alcoholic aqueous extract (extracting agent: ethanol 59% (V/V) made from the following medicinal plants:

| | |
|---|---|
| Marshmallow root (Radix Althaeae) | 0,4 g; |
| Cammomile flowers (Flores Chamomillae) | 0,3 g; |
| Horstail herb (Herba Equiseti) | 0,5 g; |
| Walnut leaves (Folia Jungladis) | 0,4 g; |
| Yarrow herb (Herba Millefolii) | 0,4 g; |
| Oak bark (Cortex Quercus) | 0,2 g; |
| Dandelion herb (Herba Taraxaci) | 0,4 g; |

*Excipients*: Ethanol 19 % (V/V), purified water.

Pharmaceutical form: Oral drops.
Clear or slightly turbid yellow-brown fluid with characteristic taste and chamomile aroma.
Turbidity or flocculation may occur during storage.

Name and address of the manufacturer.
Bionorica SE, Kerschensteinerstrasse, 11 – 15, 92318, Neumarkt, Germany.

Indications. Diseases of the upper respiratory passages (tonsillitis, pharyngitis, laryngitis). Prevention of complications and recurrences in patients with respiratory viral infections caused by the reduced resistance of the organism.

| Age | Dosage for acute symptoms | Dosage after acute symptoms have subsided and for prophylactic treatment |
|---|---|---|
| Children of 1 year of age | 5 drops 5 – 6 times daily | 5 drops 3 times daily |
| Children from 2 to 5 years | 10 drops 5 – 6 times daily | 10 drops 3 times daily |
| Children from 6 to 11 years | 15 drops 5 – 6 times daily | 15 drops 3 times daily |
| Adults and adolescents from the age of 12 years | 25 drops 5 – 6 times daily | 25 drops 3 times daily |

However, only patients from the age of 6 upwards will be included in the trial.

### 8.3.3 Reference treatment

All patients of the trial will undergo the reference treatment described below. However, only one of the two study groups (study group 1) will receive and add-on treatment with either Imupret® oral solution (see 0 and 8.3.2).

Reference treatment comprises instructions for patient's behavior as well as possible medical treatment when needed:

- Sparing diet with fractional feeding (5-6 times a day) in only small portions explicitly excluding coarse, spicy, or heavily digestible food
- At the discretion of the investigator, elimination of all factors irritating pharyngeal mucosa (e.g. thermal, chemical influence etc.)

At the discretion of the investigator, Paracetamol as single doses up to 500 mg – not more than 3-4 times daily
- At the discretion of the investigator, topical treatment like benzydamine, lidocaine (in case of severe sore throat)
- At the discretion of the investigator, antibiotic treatment in case it is indicated with e.g. amoxicillin clavulanate, cephytryaxons (in case of prescription of antibiotics patients will be evaluated separately)

### 8.3.4 Concomitant medication not allowed

Patients need to be withdrawn from the study in case of the administration of the following medication groups:

- Inhaled and systemic corticosteroids
- Interferon preparations
- Antiviral drugs
- Immunomodulators
- Antihistamines

Patients may be withdrawn following the intake of any medication which, at the discretion of the investigator, might interfere with the objectives of the trial.

## 8.4 Randomization

The clinical part of the trial will be open and randomized with no blinding procedure. Subjects will be randomly assigned to one of the two possible treatments with according to the underlying randomization list. Randomization will be performed using [StatSoft – generator of random figures] software.

The appropriate number of the randomisation schedule and associated treatment will be allocated for each subject whose entry in the randomised part of the clinical trial is confirmed. The randomisation list will be part of the trial documentation.

## 8.5 Time schedule and visits

Four scheduled visits will be performed during the first phase of the study:
First study phase

- 1 visit (1st day): screening, randomization and treatment; evaluation by Mc Isaac Score scale; LTM Scale (Local Tonsillitis Manifestation Scale): (5 symptoms: Sore throat at swallowing (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced); Sore throat at rest; Throat irritation at rest; Palatine tonsils hyperemia; Palatine tonsils edema); Patients self-assessment (VAS; 0-10)

- 2 visit (3rd±1 day): intermediate evaluation of the effectiveness of treatment - clarification of the patient's condition, the need to prescribe an antibiotic; evaluation by LTM Scale, patients self-assessment (VAS; 0-10)
- 3 visit: intermediate evaluation of the effectiveness of treatment (day 5-day ±1) via telephone (or visit if necessary); patients self-assessment (VAS; 0-10)
- 4 visit: final (10th day ±1 day). Evaluation by LTM Scale (0-15), patients self-assessment (VAS; 0-10)
- 5 Follow up; day 28: evaluation of the long-term effects of treatment
- - An unscheduled visit can be made if the patient's condition worsens (according to the patient and / or the researcher, including if the symptoms of the disease persist or worsen, including but not limited to an increase in the temperature in the armpit above 38.0 ° C at the 3rd and / or subsequent days of treatment).
- The total duration of the treatment: 10 days
- The total duration of the study for one patient is not longer than 38 days.

Any unscheduled visit may be carried out in case of worsening of the patient’s condition (at patient’s and/or investigator’s opinion), including persistence or aggravation of the disease symptoms.

# 9 PATIENTS

## 9.1 Description of recruitment procedures

Non-institutionalised healthy male or female subjects will be enrolled in the clinical trial. Recruitment may be accompanied by advertisement and patients may be contacted verbally, by telephone or in writing. Recruitment and inclusion of patients who are possibly dependent on the sponsor or an/the investigator and/or will have financial interests will be disclosed in any case.

## 9.2 Inclusion criteria

- Children (males/females), 6 - 12 years old, with severe acute tonsillitis.
- Possibility to initiate therapy within 72 hours since the onset of the disease symptoms.
- Score 4-5 according to McIsaac Scale.
- Patient's and (or) one of his/her parents' willingness and ability to fulfil the requirements of the Study Protocol.
- Signed informed consent of the patient and (or) his/her parents for participation in the study.

## 9.3 Exclusion criteria

- Score -1 to 3 according to McIsaac Scale.
- Indication for hospitalization, including:
  - purulent complications (peritonsillar abscess and others);
  - severe general condition.
- Indication for immediate initiation of systemic antibiotic therapy
- patients at risk of developing severe complications, including e.g. clinically relevant concomitant diseases of heart, lungs, kidneys, liver, neuromuscular apparatus, cancer diseases, immunosuppression, diabetes mellitus, cystic fibrosis.
- suspected infectious mononucleosis (by clinical signs);
- use of systemic antibacterial or antifungal agents, systemic glucocorticosteroids, cytostatics, immunomodulatory drugs, "interferons" or interferon derivatives during the last 14 days prior to inclusion;
- presence of haemorrhagic or pronounced necrotic process in oral cavity or pharynx, including the lymphoid ring.
- Intolerability or individual hypersensitivity to any of the study drug ingredients and the reference treatment scheme.

Patients who refuse to sign the informed consent or who do not agree to passing on of their pseudonymous data to the monitor / CRO, the sponsor, and competent national or European community authorities must not be included in this trial.

## 9.4 Premature discontinuation

### 9.4.1 Withdrawal criteria for included patients

Patients may prematurely discontinue their participation in the trial at any time, without giving reasons and without any disadvantageous consequences for their subsequent medical care.

Patients can be withdrawn from the trial by the investigator for the following reasons:

- Withdrawal of consent
- Serious Adverse Events (SAEs) at the Principal Investigator's discretion
- Appearance of non-tolerable AE(s)
- Appearance of an exclusion criterion, which concerns the safety of the patient in the opinion of the investigator
- non-adherence to the trial conditions or relevant deviations from procedures with regard to medical aspects at the Principal Investigator's discretion
- Diseases, AEs requiring treatment that occur after inclusion, which do not constitute SAEs but which, in the opinion of the Principal Investigator, would probably prevent achievement of the clinical trial objectives or which unacceptably endangered the safety of the subject
- Poor compliance of the patient
- Patient lost to follow-up
- Pregnancy (females of childbearing potential)
- Any situation judged by the investigator to be more harmful for the patient if he/she remains in the trial
- Other reasons which in the opinion of the investigator justify withdrawal of a patient (e.g. not meeting inclusion criteria during screening period)

In all cases, the reason for and date of withdrawal from the trial as well as the day and time of last intake of IMP must be recorded in the CRF and in the patient's medical records.

The investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient's records (e.g. times and dates of attempted telephone contact, documentation for sending a registered letter etc.).

### 9.4.2 Replacements

Patients withdrawn from the trial after randomization, regardless of the reason for withdrawal, will not be replaced.

### 9.4.3 Premature termination of the trial

Premature termination of a clinical trial may occur upon decision of the sponsor, the Principal Investigator, by request of an authority or because of withdrawal of positive vote by the responsible ethics committee. Furthermore, the Principal Investigator / sponsor has the right to close participating center(s) of the trial, at any time, although this can occur only after consultation between involved parties.

# 10 METHODOLOGY

## 10.1 Screening examination - Visit 1

Screening examination will be performed prior to inclusion and prior to the first intended administration of the IMP to ensure that patients are eligible for the clinical trial.

The following assessments will be performed on Visit 1 (V1):

- demographic (age, sex, ethnic origin) and anthropometric data (body weight, height, BMI)
- medical history (including prior and concomitant medication)
- physical examination vital signs (blood pressure, pulse rate, body temperature (axillar))

  Objective examination: skin and visible mucosa, palpation of abdomen and lymph nodes (submandibular, anterior and posterior cervical ones), oropharyngoscopy will be performed to assess the status of the tonsillitis.

  Hence, objective symptoms included in the "Local Tonsillitis Manifestation Scale" are assessed using a 4-point rating scale using score "0" absent, "1" mild, "2" moderate, and "3" severe/pronounced. Diagnoses will be refined by using the McIsaac Scale (see 0)
- clinical laboratory investigation: blood analysis including haematology, haemostatic system, serum chemistry, serology, urinalysis or other laboratory investigations are performed at the discretion of the investigator
- female status (in females with childbearing potential pregnancy test)

Finally, a self-assessment of the patient's throat pain by him/herself and (or) his/her parent(s) using a visual analogue scale (VAS) is performed.

All data has to be documented by the investigator in the patient's medical file and recorded in the CRF. Afterwards, inclusion and exclusion criteria are checked by the investigator, documented in the patient's medical file, and recorded in the CRF.

At the end of Visit 1 the patient will be randomized, sorted to one of the two study groups and IMP will be handed over.

## 10.2 Status evaluation - Visit 2

The next status evaluation of the disease will be performed on day 3, i.e. ± 1 day after Visit 1 (V1).

A physical examination of vital signs (blood pressure, pulse rate, body temperature (axillar)) will be performed. All physical examinations done at V1 including skin and visible mucosa, palpation of abdomen and lymph nodes, oropharyngoscopy will be repeated to assess the status of the tonsillitis.

Again, objective symptoms included in the "Local Tonsillitis Manifestation Scale" are assessed and diagnoses will be refined by using the McIsaac Scale (see 0).

Checks for general well-being (AE-checks), checks of restrictions and medication will be performed.

The investigator will estimate indicators for prescription of antibiotics and will decide whether a patient will remain on the study treatment or not. If an antibiotic agent is prescribed, details will be documented and the patient will be instructed about the mode of administration. Intake of

antibiotic drug will be documented in the CRF. Patients with intake of antibiotics will be evaluated separately. At the discretion of the investigator the patient may be advised not to take IMP anymore. If so, this will be documented as well.

Self-assessment of the patient's throat pain by him/herself and (or) his/her parent(s) using a visual analogue scale (VAS) is performed afterwards. Moreover, forms for VAS assessment will be handed over to the patient. The patient will have to assess his/her sore throat every study day until visit 4 on study day 10±1.

## 10.3 Interim evaluation of treatment efficacy- Visit 3

Visit 3 (V3) will be performed on day 5 ±1 by a telephone call.

Intermediate evaluation of the effectiveness of treatment (day 5-day ±1) via telephone (or visit if necessary); patients self-assessment (VAS; 0-10)

## 10.4 Treatment efficacy, end of Reference treatment - Visit 4

At visit 4 (V4) on day 10 ±1 the status of the disease will be again evaluated.

A physical examination of vital signs (blood pressure, pulse rate, body temperature (axillar)) will be performed. All physical examinations done at V1 including skin and visible mucosa, palpation of abdomen and lymph nodes, oropharyngoscopy will be repeated to assess the status of the tonsillitis.
Again, objective symptoms included in the "Local Tonsillitis Manifestation Scale".
Checks for general well-being (AE-checks), checks of restrictions and medication will be performed.

Self-assessment of the patient's throat pain by him/herself and (or) his/her parent(s) using a visual analogue scale (VAS; 0-10 points) is performed. Forms of VAS assessment will be collected from the patient.

## 10.5 Treatment efficacy, end of treatment - Visit 5

Visit 5 (V5) will be performed on day 28 by a telephone call (for bough the groups).

Checks for general well-being (AE-checks), checks of restrictions and medication will be performed.

## 10.6 Clinical assessments and parameters

Assessment of tonsillitis will be performed according to the Local Tonsillitis Manifestation Scale. In detail the following symptoms will be investigated:

Local Tonsillitis Manifestation Scale

- Sore throat at swallowing (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced);
- Sore throat at rest, i.e. during the intervals between swallowing acts (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced);
- Throat irritation at rest, i.e. during the intervals between swallowing acts (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced);
- Cough associated with throat discomfort (0 – absent, 1 – mild, 2 – moderate, 3 – severe / troublesome).
- Posterior pharyngeal wall hyperaemia (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced);
- Palatine tonsils hyperaemia (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced);
- Palatine tonsils oedema (0 – absent, 1 – mild, 2 – moderate, 3 – severe / pronounced).

**Diagnoses will be further refined using the McIsaac Scale**

| Symptom | Score |
|---|---|
| Body temperature exceeding 38°C | +1 |
| Absence of cough | +1 |
| Painful anterior cervical lymph nodes | +1 |
| Tonsillar oedema and/or exudate on tonsils | +1 |
| Age 3–14 years old | +1 |
| 15–44 years old | 0 |
| >45 years old | - 1 |

Assessment of type of tonsillitis:
Score 0 – probability of group A β-haemolytic streptococcus (GABHS) infection is 1-2%;
Score 1 – probability of GABHS infection is 5-10%;
Score 2 – probability of GABHS infection is 11-17%;
Score 3 – probability of GABHS infection is 28-35%;
Score 4 – probability of GABHS infection is 51-53%;

**Self-assessment of the quality of life by the patient.**

o Sore throat at swallowing (0 –10 points VAS);
o Sore throat at rest, i.e. during the intervals between swallowing acts (0 –10 points VAS);
o Throat irritation at rest, i.e. during the intervals between swallowing acts (0 –10 points VAS);
o Cough associated with throat discomfort (0 –10 points VAS).

## 10.7 Appropriateness of measurements

All methods used for efficacy and safety assessments are standard methods for which reliability, accuracy and relevance have been documented (e. g. vital signs, body temperature, urine dip sticks etc.).

## 10.8 Handling and documentation of clinical data

The Principal Investigator has to ensure that all data required according to this protocol will be entered promptly in the patient's file, raw data sheets or directly in the CRF.

Co-ordinating Investigator, a member of the trial team will check data in the CRFs for formal correctness, completeness and legibility of the entries.

Documentation on clinical raw data, i.e. documentation on VAS will be collected on personal visits. A member of the trail team will check these raw data for formal correctness, completeness and legibility of the entries.

Entries on CRFs must be made with a black ball-point pen and must be legible. Pencils and correction fluids are not to be used. If corrections are necessary, they will be entered by a member of the trial team in the following manner: the wrong CRF entry will be crossed out; however, it must remain legible, and the correct entry will be placed next to the wrong entry. Changes and corrections to a CRF will be initialled and dated. For changes and corrections of direct CRF entries a reason must be provided, except in case of self-explanatory correction.

## 10.9 Risks related to the participation in the clinical trial

Blood withdrawal might occur during the study at the discretion of the investigator. Blood withdrawal might be painful or the subjects might temporarily become dizzy. Subjects may also experience intermittent complaints like re-bleeding or puncture site bruises, blood clot (thrombus) in the punctured vessel (rarely), puncture site infections (rarely) or mechanical nerve damage (very rarely)

### 10.9.1 Procedure related risks

### 10.9.2 Risks related to the investigational medicinal product

Imupret® oral drops

The investigational products Imupret® oral drops contain the ingredients given in sections 0 and 8.3.2.
According to the Summaries of Product characteristics the following site effects and interactions may occur during intake:

Side effects
Rarely gastrointestinal disorders (e.g. abdominal pain, nausea, vomiting) may occur. Allergic reactions (e.g. rash, itching, dyspnea) may also occur.

When taken together with preparations containing matricaria flowers and also in patients with hypersensitivity to other plants of the Composite family (e.g. Yarrow herb (Achillea Millefolium)) allergic reactions may occur. In case of any undesirable side effects the use of the medicinal product should be discontinued and a doctor should be consulted.

Interactions with other medicines and other forms of interaction
No interactions with other medicines have been reported. When using preparations which contain oak bark, the resorption of alkaloids and other alkaline medicinal agents may be reduced or blocked if taken together.

Overdose
No cases of intoxication due to overdose has been reported.

Reference treatment

At the discretion of the investigator, Paracetamol as single doses up to 500 mg – not more than 3-4 times daily will be prescribed. Moreover, at the discretion of the investigator, topical treatment with e.g. benzydamine, lidocaine (in case of severe sore throat) may be prescribed. In

case an antibiotic treatment will be necessary, the investigator may prescribe e.g. amoxicillin clavulanate, cephytryaxons etc.

As it is not yet known, what kind of prescription will be exactly done by the investigator, possible side effects and interactions are hardly to be described in here in the protocol. In any case the investigator has to inform the patient and (or) his/her parent(s) about the risks related to the intake of Reference medication according to the respective Summaries of Product Characteristics.

# 11 SAFETY ASPECTS

## 11.1 Definitions

### 11.1.1 Adverse event [AE]

An Adverse Event [AE] is defined as any untoward medical occurrence in a clinical trial subject to whom an Investigational Medicinal Product [IMP] has been administered and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, refer to section 11.5), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

***Examples of an AE include:***

- A new sign, symptom, illness, or syndrome;
- Worsening of a pre-existing condition including either an increase in severity and/ or frequency of existing symptoms to a clinically significant exacerbation or the appearance of a new symptom during the AE reporting period;
- An effect of the IMP, including comparator or of concomitant medication;
- Signs, symptoms, or the clinical sequelae of a suspected interaction;
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication;
- An effect of a procedure required by the protocol;
- An accident or injury.

***Examples of an AE do <u>not</u> include:***

- A pre-existing condition, i.e. illnesses, clinical signs or symptoms, and/ or pathological laboratory values, which were already present at the first examination, unless an atypical course of the disease with exacerbation or increase in incidence of symptoms is observed;
- Medical or surgical procedures (e.g. endoscopy, appendectomy);
  In general, these comprise therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected during the clinical trial. Planned surgical measures and the condition(s) leading to these measures are not AEs if the condition was known before the period of observation. In the latter case the condition should be reported as medical history.
- Worsening or deteriorations of common symptoms of the disease under study and/ or other expected clinical outcomes of the disease under study will generally not be recorded as AE.

AEs fall into the categories ‘non-serious’ or ‘serious’ (refer to section 11.1.2).

### 11.1.2 Serious adverse event [SAE]

A Serious Adverse Event [SAE] is an AE that at any dose (including overdose):

- results in death;
- is life-threatening[1];
- requires inpatient hospitalisation or prolongation of existing hospitalisation[2];

- results in persistent or significant disability or incapacity[3];
- is a congenital anomaly or birth defect;
- is a medical important event[4].

1 'Life-threatening' means that the subject is at immediate risk of death at the time of the SAE; it does not refer to an AE which hypothetically might have caused death if it were more severe.

2 Hospital inpatient admission (for more than one calendar day) or prolongation of a hospital stay by at least one calendar day are required for the treatment of the AE, or occurs as a consequence of the AE.

***Hospitalisation does <u>not</u> include the following***:

- Emergency room/ accident and emergency/ casualty department visits;
- Out-patient/ same-day/ ambulatory procedures;
- Observation/ short-stay units;
- Rehabilitation facilities/ health resorts;
- Hospice facilities;
- Respite care (e.g. caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Custodial care facilities;
- Clinical research/ phase I units;
- Hospitalisation in the absence of a precipitating, clinical AE:
    - Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of a pre-existing condition (e.g. for work up of persistent pre-existing lab abnormality);
    - Social admission (e.g. patient has no place to sleep);
    - Administrative admission (e.g. for annual physical examination);
    - Optional admission not associated with a precipitating clinical adverse event (e.g. for elective cosmetic surgery).

3 'Persistent or significant disability or incapacity' means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

4 Medical and scientific judgement should be exercised in deciding whether immediate reporting is appropriate in other situations where none of the serious criteria above are met. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered 'serious'. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation, or development of drug dependency or drug abuse.

***Difference between 'severe' and 'serious'***

The term 'severe' is often used to describe the intensity (severity) of an event (as in mild, moderate, or severe myocardial infarction). The event itself, however, may be of relatively minor medical significance (e.g. severe headache). This is not the same as 'serious', which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 11.1.3 Adverse reactions [AR]

An adverse reaction [AR] is any noxious and unintended response to an IMP irrespective of the dose administered. The phrase 'response to an IMP' means that a causal relationship between

the administration of the IMP and the occurrence of an AE is at least a reasonable possibility (refer to section 11.3).

All AEs will be judged by either the investigator or the sponsor as ‘related’ or ‘not related’ to the IMP.

An unexpected AR is an AR for which the nature or severity is not consistent with the applicable reference safety information for the Imupret® or Reference treatment provided in the Summaries of Product Characteristics.

When an unexpected AR also meets the definition of a SAE (refer to section 11.1.2), it is considered an unexpected serious AR. The co-ordinating investigator will report all suspected unexpected serious adverse reactions [SUSAR] to competent authorities, ethic committees, investigational sites, Bionorica SE as the supporter of this trial and other relevant recipients in all participating countries, in accordance with applicable reporting requirements.

### 11.1.4 Alert terms and other reasons for expedited reporting to Pharmacovigilance

No special events are to be reported as alert terms in this trial.

## 11.2 Period of observation

For the purpose of this trial, the period of observation for collection of AEs extends from signing of the informed consent form until the end of the trial (including follow-up period).

The investigator is not expected to actively monitor subjects for AEs once the clinical trial has ended. However, if the investigator becomes aware of a SAE in a subject after the end of the period of observation (regardless of the time elapsed from the trial end), and considers the event possibly related to prior trial treatment or procedures, the investigator should contact the Drug Safety department of Bionorica SE to determine how the AE should be documented and reported.

Regardless of the individual duration of the trial, any AE (including abnormal laboratory findings), irrespective of severity and whether serious or not, must be monitored by the investigator until it has satisfactorily subsided or has stabilized to such an extent that further marked improvement can no longer be expected or until a satisfactory medical explanation is found. The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject’s records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

This also applies to AEs still ongoing at the last visit of the individual patient. If necessary a further visit must be scheduled by the investigator.

It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow – up procedures are performed.

## 11.3 Assessment and recording of adverse events

The occurrence of AEs will be assessed by non-directive questioning of the subject at each visit. Further, AEs volunteered by the subject during or between visits or detected through observation, physical examination, laboratory test or other assessments will be documented. AEs that were ongoing at the end of the previous visit should be queried for resolution or change in severity or seriousness.

Clinical trial subjects will be instructed by the investigator to report any AEs, subjective complaints or objective changes in their well-being to the investigator or the clinic personnel, regardless of the perceived relationship between event and IMP.

**All AEs** (whether serious or non-serious, or considered as an alert term) must be documented.

In case of a **SAE** (refer to section 11.1.2), the investigator must additionally complete a 'SAE report form' at the time the SAE is detected. This form will be immediately send to the Drug Safety department of Bionorica SE as detailed in section □.

For each AE the following data will be recorded in the CRF:

- **Description of the AE** in medical terms (preferably: diagnosis), not as reported by subject.

  Note: Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent a typical or extreme manifestation of the diagnosis, in which case they should be reported as separate AE.

- Date of onset (start date) and date of recovery (stop date).
- **Intensity of the AE** as assessed by the investigator as follows:
  - ***Mild*****:** The AE is easily tolerated and does not interfere with routine activities/ normal functioning of the subject.
  - ***Moderate*****:** The AE causes discomfort and affects the subject's normal activities, i.e. interferes with routine activities, but are not hazardous, uncomfortable or embarrassing to the patient.
  - ***Severe*****:** The AE causes considerable interference with the subject's usual activities, e.g. inability to work.
- **Causal relationship of the AE** to the IMP according to the available data as:
  - ***Related*****:** There is a reasonable causal relationship, which means that there is evidence to suggest a causal relationship. The adverse event could medically (pharmacologically/ clinically) be attributed to the investigational product under trial in this protocol.
  - ***Not related:*** There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The adverse event could not medically (pharmacologically/ clinically) be attributed to the investigational product under trial in this protocol.
- **Actions taken on the IMP**:
  - e.g. drug withdrawn, dose reduced, dose increased, dose not changed, permanently discontinued, temporarily discontinued and reintroduced, unknown, not applicable (e.g. AE occurred in IMP-free period)
- Other actions taken due to the AE:
  - e.g. corrective treatment
- **Outcome of the AE**, e.g.:
  - ***Recovered/ resolved***: The AE had stopped completely and the stop date is recorded.
  - ***Recovered/ resolved with sequelae***: No further changes are expected due to the AE and residual symptoms are assumed to persist.
  - ***Not recovered/ not resolved***: The AE is ongoing; the event is followed up.
  - ***Fatal***: The subject died as a consequence of the AE; date of death is recorded as stop date of the AE.
  - ***Unknown***: Unknown to the investigator (e.g. patient lost to follow up).

- **Seriousness** according to definition in section 11.1.2.

## 11.4 Reporting of SAE

Any SAE and AE that fulfil a reason for immediate reporting (as defined in section 11.1.4) will be reported immediately (within 24 hours after receipt) to the responsible ethics committee and authority according to the obligations of the Ukraine (online to State Expert Center MH).

Moreover, within 15 days after receipt by the investigator via telephone, fax or e-mail to the Drug Safety department of Bionorica SE:

**Bionorica SE**
**Drug Safety**
**Phone: +49 9181 231 7200**
**Fax: +49 9181 231 6 7200**
**E-mail: drugsafety@bionorica.de**

The initial report must be as complete as possible. The report should include at least the following information:

- **Clinical trial subject identification** (e.g. assigned subject number, age or year of birth, gender)
- **Identifiable reporting source** (e.g. centre number, name of investigator, telephone number, fax and/ or e-mail address)
- **Identification of the clinical trial** (e.g. trial code) or IMP
- **SAE term** (preferably: diagnosis; if possible, also including description and course of the SAE)
- **Seriousness criterion** (refer to section 11.1.2)
- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data as defined in 10.2. If based on follow-up information the investigator changes his/her initial causality assessment, this should be submitted to the Drug Safety department of Bionorica SE immediately (i.e. within 24 hours after receipt) by using the SAE report form.
- **Signature of the investigator**

Following a report by phone, written information has to be sent by fax or e-mail to the Drug Safety department of Bionorica SE within two working days. When necessary an 'SAE Report Form' will be accompanied by relevant pages from the CRF, e.g. for medical history, AEs or concomitant medication (online-form in official site of State Expert Centre MH).

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the 'SAE report form'. Information not available at the time of the initial report (e.g. an end date for the SAE or laboratory values received after the report) will be documented on a follow-up 'SAE report form' and reported within 15 days after receipt to the Drug Safety department of Bionorica SE.

Additional information not covered by an 'SAE Report Form', including copies of hospital reports, autopsy reports or other relevant documents, will be requested, if necessary, by either the monitor or the Drug Safety department of Bionorica SE for a detailed description and a final evaluation of the case. All personal identifiers (e.g. name, detailed birth of date) must be pseudonymized prior to submission by blinding personal data and using the assigned identification code of the subject.

The investigator should institute any supplementary investigations of SAE based on their clinical judgement of the likely causative factors. This may include seeking further opinion from a specialist in the field of the SAE. Bionorica SE may also request extra tests.

If the SAE information is incomplete or inconsistent and directly affects the sponsor's reporting obligation to health authorities, the Drug Safety department may directly contact the investigator for clarification.

The sponsor will be responsible for notification of the competent authorities, ethics committee(s) and investigators in the event of a SUSAR and any other important safety issues requiring expedited reporting, in accordance with the applicable legislation.

## 11.5 Abnormal laboratory parameters

Abnormal laboratory findings (e.g. clinical chemistry, haematology, or urinalysis) or other abnormal assessments (e.g. vital signs) will be judged by the investigator as 'clinically relevant' or 'not clinically relevant' based on the investigator's medical and scientific expertise. Abnormal, clinically relevant results should be verified to rule out laboratory error.

Clinically relevant, abnormal findings or other clinically relevant abnormal assessments that are detected during the clinical trial or that were present at baseline and significantly worsen during the trial will be recorded as AE. However, clinically relevant abnormal laboratory findings or other abnormal assessments that are associated with a medical condition already documented as medical history or AE will not be recorded separately, unless judged by the investigator as more severe than expected for the subject's condition.

If during treatment with an IMP abnormal laboratory findings occur which were not present at baseline and which were judged by the investigator as 'clinically relevant' and recorded as AE in the CRF, the investigator is responsible to carry out further clinical or laboratory tests until the values return to the normal range or until a plausible explanation is given by the investigator (e.g. disease).

## 11.6 Handling of pregnancies

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this clinical trial. The investigator will inform Bionorica about pregnancy department of Bionorica SE within 15 days after acknowledgment of a subject's pregnancy).

Any subject who becomes pregnant while participating in the trial should discontinue treatment and will be withdrawn from the trial.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Generally, follow-up will be no longer than 3 months following the estimated delivery date.

Newly diagnosed pregnancy in a clinical trial subject is not considered to be an AE or SAE unless meeting seriousness criteria, or it is suspected that the IMP interacted with a contraceptive method and led to pregnancy.

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Furthermore, any SAE occurring as in association with a pregnancy (in cases where the pregnancy occurred after the end of the trial participation of the subject) brought to the investigator's attention after the subject has completed the trial and considered by the investigator as reasonably related to the IMP must be promptly reported to the sponsor.

# 12 EVALUATIONS

## 12.1 Data Management

Data management comprises the following general processes in chronological order: Set-up of database, data entry and cleaning including query handling, coding procedures, data validation and final review of data.
Upon receipt of CRFs and respective raw data sheets, the data from the CRFs will be entered and transferred into the trial data base. Data base will be prepared for data entry and will reflect the final version of the CRF and raw data sheets. Adequate quality control methods will be applied. Identified discrepancies, will be queried by a responsible data manager using data clarification forms and forwarded to the investigator. Data sets and data base will be hard locked after all discrepancies are resolved and the analysis sets of subjects are documented. In case, that the data base has to be opened, this will be done only after agreement with all involved parties. All changes after data base hard lock will be tracked. All clinical data included in the data base will at least be listed.

For data coding (e.g. AEs, medical / surgical history, medication) internationally recognized and accepted dictionaries will be used (Medical Dictionary for Regulatory Activities (MedDRA) for AEs and WHO-dictionary for medication). In general, the latest version of medical dictionaries valid at data base setup will be used for coding throughout the clinical trial.

## 12.2 Statistical evaluation

The statistical planning of the trial and the statistical analyses will be conducted following the principles specified in the ICH Topic E9 (ICH, 1998), and will be carried out by a qualified statistician in accordance with the ICH. Technical details of the statistical analyses will be specified prior to data analyses.

In general, there will be one main statistical evaluation.

Data base will be closed after all data are entered and cleaned.

In general, unless otherwise stated, continuous data will be summarized by means of descriptive statistics (mean, standard deviation (SD), median, quartiles, minimum, and maximum). Categorical variables will be described in contingency tables as absolute number and percentages.

AEs will be evaluated considering frequency and intensity. Furthermore, AEs will be evaluated considering relationship to the IMP, outcome, and seriousness. Both will be described by absolute and relative frequency. Descriptive statistics will be calculated for clinical laboratory parameters determined. Frequencies of values inside and out of normal range (i.e. above and below) will be given where possible.

This is an exploratory trial with no formal sample size estimation. Therefore, beneath descriptive statistics of efficacy endpoints, concluding statistics may be performed in a data driven way, in order to find clinically relevant differences between study participants, time points and treatments. Possible corrections to prevent an alpha inflation will be performed, if meaningful.

Specifications of the biometrical evaluation will be defined after all data management processes of the study phase will be terminated and data base was closed. In general, variables will be analyzed considering the underlying analysis set, treatment and time point, if meaningful.

### 12.2.1 Analysis sets

Full Analysis Set (FAS)

The FAS consists of all randomized patients with at least one documented application of IMP and with at least one observed post-baseline value.

Per Protocol Set (PPS)

The PPS consists of all patients of the FAS without major protocol deviations. The evaluation of protocol deviations and whether they lead to the exclusion of a patient from the PPS will be performed during data review of the study.

### 12.2.2 Primary endpoint

Main criterion for evaluation in the trial will be:

- Scores determined by the Local Tonsillitis Manifestations Scale refined by McIsaac's scale. Scores will be dichotomized to decide for two categories (therapy effective/therapy ineffective).
  Scores will be evaluated by treatment and time point, i.e. per visit
- Need for an antibacterial therapy, i.e. number of patients per treatment.

### 12.2.3 Secondary endpoints

- Scores/Intensity of each underlying disease symptom assessed by the Local Tonsillitis Manifestations Scale by treatment and time point, i.e. per visit
- Axillary temperature per treatment and measurement time point
- Patient's self-assessments on VAS per treatment and measurement time point
- Self-assessment of the symptoms by the patient.

### 12.2.4 Safety evaluation

AEs will be evaluated considering frequency and intensity. Furthermore, AEs will be evaluated considering relationship to the IMP, outcome, and seriousness. Both will be described by absolute and relative frequency. Descriptive statistics will be calculated for clinical laboratory parameters determined. Frequencies of values inside and out of normal range (i.e. above and below) will be given where possible.

# 13 RECORD KEEPING

The investigator will maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified according to the international legal requirements or according to the local applicable regulatory requirements.

## 13.1 Documentation of patients' participation

Patient clinical source documents include, but are not limited to, patient clinic records, physician's and nurse's notes, appointment book, original laboratory reports, imaging diagnostic, pathology and special assessment reports, consultant letters, etc.

## 13.2 Data protection

## 13.3 Essential documents at trial center

Essential documents related to the clinical trial will be retained in the Trial Master File and patient clinical source documents.
The Trial Master File will contain the clinical protocol/protocol amendments, sample of eCRF printout, ECs/IRB and regulatory authorities' approval with correspondence, original initialed and dated PI as well as the signed IC, sample PI sheet and IC form, trial medication records, investigator's curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per ICH-GCP and local regulations.

## 13.4 Archiving

Documents must be kept on file by the investigator for 15 years. If source documents are not durable as long as needed (e.g. printouts on thermo labile paper), they must be preserved as certified copy.

# 14 QUALITY ASSURANCE

Domestic and foreign regulatory authorities, the ECs/IRB, and an authorized auditor may request access to all source documents, CRF, and other trial documentation for on-site audit or inspection. Audits and inspections can be conducted at any time during or after the trial to assure the validity and integrity of trial data.
Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other trial documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

# 15 LEGAL AND BUSINESS MATTERS

## 15.1 Insurance for patients

Liability and insurance provisions for patients will be arranged according to legal requirements. In accordance with the applicable national laws of each participating country and GCP, the sponsor has effected a patient insurance. The investigator will receive a copy of the insurance certificate as well as of the corresponding insurance conditions prior to the start of the study. Following the clauses of the contract, the patients have to be informed about the existence of the insurance contract and about their obligations.
Liability and insurance provisions for patients and investigators participating in this trial are given in separate agreements.

## 15.2 Contracts, finances

Before the start of the trial, the investigator will disclose any proprietary or financial interests he or she might hold in the investigational products as outlined in a ‘financial disclosure form’ prepared for this trial. The investigator agrees to update this information in case of significant changes during the trial. Similar information will be provided by each sub-investigator to whom the investigator delegates significant trial related responsibilities.

## 15.3 Disclosure of all information and results

All information concerning the results derived from the trial and the investigational product are regarded as confidential. The investigators and members of their research teams are not permitted to disclose any such information without prior written approval as long as the data are unpublished. By his signature the investigator(s) agree(s) to keep the data confidential.

# 16 REGULATORY AND ETHICS

## 16.1 Good Clinical Practice

This trial is to be conducted according to globally accepted standards of GCP (as defined in the ICH E6 R2 Guideline), in agreement with the Declaration of Helsinki from 2013 and in keeping with local regulations. The investigator should ensure on an ongoing basis that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions. Minutes of trial team meetings and documentation of trial team training should be maintained in the trial investigator site file.
The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he/she has delegated significant trial-related duties.
Serious GCP breaches or serious protocol deviations mean a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical trial.

## 16.2 Subject information and informed consent

Every trial participant will receive a complete and comprehensive explanation of the significance, nature, extent and possible risks of the trial. To this end a detailed, written sheet will be made available. In addition, the investigator will carry out an oral information session during which the patients will be given sufficient time and opportunity to clarify remaining questions. The investigator has to document his/her conversation with the patient with date, duration of the conversation, main contents, questions and answers in patient's medical file. In addition, the investigator has to document in the patient's file that the patient is enrolled into the trial.

The investigator will inform the patient or his/her legal representative(s) that his/her consent to participation can be withdrawn at any time without giving any reason and that no disadvantages will result concerning further medical treatment. Neither the investigator nor the site staff should coerce or unduly influence a patient to participate or to continue to participate in the trial.

The patient information sheet has to be initialed and dated by the patient and/or his/her legal representative(s) to confirm comprehension. Afterwards, the patient and the investigator will sign and date the Informed Consent form personally. The original initialed and dated patient information as well as the signed Informed Consent Form will be archived in the Trial Master File. The patient will receive the second original of the patien information and signed Informed Consent Form.

The investigator is responsible for correctly obtaining the Informed Consent in accordance with the applicable regulatory requirement(s), GCP and the ethical principles that have their origin in the Declaration of Helsinki. A signed Informed Consent form must be obtained prior to initiation of any trial-specific procedures. Date and time of signature must be documented. The record of the Informed Consent must be available for an audit by competent authorities (CAs) whenever requested. The patient will be informed about any changes in the trial protocol due to substantial protocol amendments and will be asked to sign an amended patient information sheet and Informed Consent form accordingly.

# 17 PUBLICATION POLICY

Publication of trial results requires a mutual agreement between the investigator(s) and Bionorica SE. Any publication of the trial data by the sponsor or investigator(s) will wholly be consistent with the integrated report in accordance with the ethical principles of the Declaration of Helsinki.

# 18 REFERENCES


1. Kommission E (1984, 1990). Monographie Matricariae flos (Kamillenblüten), inkl. Berichtigung. Bundesanzeiger Nr. 228 vom 05.12.1984, Bundesanzeiger Nr. 50 vom 13.03.1990, Bundesinstitut für Arzneimittel und Medizinprodukte.
2. Kommission E (1986). Monographie Equiseti herba (Schachtelhalmkraut). Bundesanzeiger Nr. 173 vom 18.09.1986, Bundesinstitut für Arzneimittel und Medizinprodukte.
3. Kommission E (1989). Monographie Althaeae radix (Eibischwurzel). Bundesanzeiger Nr. 43 vom 02.03.1989, Bundesinstitut für Arzneimittel und Medizinprodukte.
4. Kommission E (1990). Monographie Achillea millefolium (Schafgarbe). Bundesanzeiger Nr. 22 a vom 01.02.1990, Bundesinstitut für Arzneimittel und Medizinprodukte.
5. Kommission E (1990). Monographie Juglandis folium (Walnußblätter). Bundesanzeiger Nr. 101 vom 01.06.1990, Bundesinstitut für Arzneimittel und Medizinprodukte.
6. Kommission E (1990). Monographie Quercus cortex (Eichenrinde). Bundesanzeiger Nr. 22 a vom 01.02.1990, Bundesinstitut für Arzneimittel und Medizinprodukte.
7. Kommission E (1992). Monographie Taraxi herba (Löwenzahnkraut). Bundesanzeiger Nr. 162 vom 29.08.1992, Bundesinstitut für Arzneimittel und Medizinprodukte.
8. Webb JL. Effect of more than one inhibitor. Enzyme and metabolic inhibitors. 1. New York: Academic Press; 1963, p. 66–79 (488–512).
9. Maier, M. and A. Maier (1974). "Erkrankungen des lymphatischen Rachenringes - 10jährige Erfahrungen einer Gemeinschaftspraxis für HNO-Erkrankungen." Z Allgemeinmed 50(26): 1150-1152.
10. Sprenger, F. (1975). "[Conservative treatment of chronic tonsillitis]." Z Allgemeinmed 51(33): 1549-1551.
11. Berger T. Verträglichkeit und Wirksamkeit eines pflanzlichen Kombinationspräparats. MMW-Fortschr. Med. II/2008 (150), p. 85-90
12. Vavilova V., Abramov-Sommariva D., Steindl H., Wonnemann M, Ryzhova E., Rusova T., Lebedenko A., and Kolchenko I. Effectiveness and tolerability of Tonsilgon® N in the treatment of recurrent upper respiratory tract infections in children: A non-interventional study in Russia, Clinical Phytoscience (2016) (submitted)