TITLE PAGE

STATISTICAL ANALYSIS PLAN

Of 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:
ATi-2

Imupret in tonsillitis
Clinical phase: IV
Date: 07.02.2019

Name of the investigational product: Imupret®

Coordinating Investigator: Prof. Dr. Vasyl Ivanovych Popovych

Sponsor:
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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.

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.

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.

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.

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.