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Wissenschaftliche Dienstleistungen
Scientific Services

A randomised, open, controlled pilot study to investigate the potential of Buparid/PARI SINUS versus Budes® Nasal Spray to avoid or postpone sinus surgery in adult patients with Chronic Rhinosinusitis (CRS)

Project ID: 12082.102
EudraCT No.: 2013-002421-30

Statistical Analysis Plan

Version: 1.0

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Prepared for

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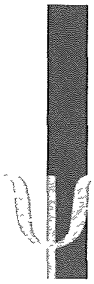
Abbreviations

AE	Adverse event
ATC	Anatomic Therapeutic Chemical classification
CRF	Case report form
CRS	Chronic rhinosinusitis
DMP	Data management plan
DRM	Data review meeting
EAS	Endoscopic Appearance Score
FAS	Full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
PDF	Portable Document Format
PNIF	Positive Nasal Inspiratory Flow
PPS	Per-protocol analysis set
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SNOT	Sino-Nasal Outcome Test
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
WHO	World Health Organization



1 Protocol summary

1.1 Title

A randomised, open, controlled pilot study to investigate the potential of Buparid/PARI SINUS versus Budes® Nasal Spray to avoid or postpone sinus surgery in adult patients with Chronic Rhinosinusitis (CRS) (Project ID: 12082.102; EudraCT No.: 2013-002421-30)

1.2 Applicable documents

- Clinical trial protocol, amended version 2 of 17 July 2015
- Data Management Plan (DMP), version 1.0 of 19 November 2019
- Psy Consult Scientific Services biometry SOPs

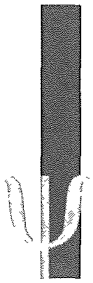
1.3 Objectives, design, endpoints, schedule

This is a randomized, open-label, active-controlled pilot study that compares the efficacy and safety of Buparid/PARI SINUS versus Budes® Nasal Spray in the treatment of chronic rhinosinusitis (CRS) without polyposis nasi in adult patients, with the therapeutic objective of avoiding or postponing sinus surgery. The objective of the study is to obtain data for the selection of a clinically relevant primary endpoint to compare the efficacy and safety of the investigational treatments in patients with CRS.

Patients meeting the inclusion and exclusion criteria are randomized to eight weeks' inhalation treatment with the investigational products. It is planned to randomize and treat a total of 20 (2 x 10) patients in 3 centers.

The study schedule starts with a screening visit (Visit 0) performed about one week before randomization. Visit 1 is the baseline visit at which eligible patients are randomized and start the investigational treatment and the baseline values of the applicable outcome measures are obtained. Additional visits are scheduled after 4 (Visit 2), 8 (Visit 3; end of treatment), 12 (Visit 4), 24 (Visit 4), and 48 weeks after baseline (Visit 6).

Efficacy is assessed using the following endpoints:



Health-specific quality of life (at Visits 0, 1, 2, 3, 4, 5 and 6):

- SNOT 20 (Sino-Nasal Outcome Test 20)

Nasal obstruction (at Visit 0, 1, 2 and 3):

- Rhinonanometry (PNIF, Positive Nasal Inspiratory Flow)
- Nasal obstruction

Inflammation of the nasal mucosa and paranasal sinus (Visits 2 and 4):

- Magnetic Resonance Imaging
  - Thickness of mucosa
  - Lund-Mackay-Score

Endoscopy (at Visits 0, 3 and 6):

- Endoscopic Appearance Score (EAS)

Symptoms of rhinosinusitis (at Visits 0, 1, 2, 3, 4, 5 and 6):

- Rhinorrhea
- Facial pressure pain by means of a Visual Analogue Scale

Loss of taste/Loss of smell (at Visits 0, 1, 3 and 6):

- Taste strips
- Sniffing sticks

In accordance with the design of the trial as a pilot study no pre-defined distinction between primary and secondary endpoints has been made.

Safety is assessed based on treatment-emergent adverse events (TEAEs). Adverse events (AEs) are considered to be treatment-emergent if they occur after the first administration of an investigational treatment.

2 Responsibilities, Standard Operating Procedures

Pari Pharma GmbH is responsible for reviewing and approving this SAP and for contributing to the data review meeting (DRM), including review and approval of the meeting minutes.

Psy Consult Scientific Services is responsible for developing, programming, and performing the planned statistical analyses, and for providing the results as PDF files.

Psy Consult Scientific Services biometry SOPs apply.

3 Statistical analyses

3.1 General concept

This is the first study using the drug/device combination Buparid/PARI SINUS for treatment of CRS without polyposis nasi. It is therefore intended to be a proof-of-concept study with the aim of exploring the therapeutic potential of the novel drug/device combination in this indication as well as of assessing several efficacy outcome measures for their suitability to discriminate between different treatments in order to enable the selection of an appropriate primary endpoint for a confirmatory study intending to demonstrate therapeutic benefit.

In accordance with the exploratory objectives of the trial, the statistical concept will be purely descriptive, and treatment group comparisons will be based primarily on confidence intervals, particularly as the study has not been powered for a confirmatory proof of a clinically meaningful effect.

3.2 Analysis populations

Safety analysis set (SAS) – The SAS is defined as all patients randomized who receive the investigational treatment at least once.

Full analysis set (FAS) – The FAS is defined as all patients randomized who receive the investigational treatment at least once, and who provide any post baseline data for treatment efficacy.

A Data Review Meeting may decide to exclude patients from the FAS in cases of very severe protocol violations seriously interfering with the assessment of treatment efficacy (e. g., patients not suffering from the condition under investigation).

Per protocol set (PPS) – The PPS is defined as all patients included in the FAS

- who complete randomized treatment as scheduled, or who are withdrawn from treatment prematurely for lack of efficacy or for lack of tolerability, *and*
- for whom no major protocol deviations interfering with the assessment of treatment efficacy are observed.

Eligibility for the analysis data sets will be determined in a data review meeting (DRM) held after closing the database but before performing any analyses broken down by treatment group. Protocol violations will be classified as 'major' when a significant influence on the assessment of treatment efficacy cannot be excluded. Comprehensive justification for the classification of a protocol violation as 'major' will be given in the DRM meeting minutes as well as in the integrated clinical study report, both of which will also identify the patients who will be excluded from any of the analysis data sets, together with the reasons for their exclusion.

With due regard to the principles if Intention to Treat the analysis of treatment efficacy will be performed in the FAS. Additional efficacy analyses will be performed in the PPS to provide sensitivity analyses which assess the efficacy of the investigational products in the absence of important protocol deviations. Any data referring to safety and tolerability will be analyzed in the SAS.

3.3 Statistical and analytical methods

The study data will be analyzed in accordance with the concept of descriptive data analysis. Continuous/quantitative data will be summarized in accordance with their applicable level of measurement, by specifying summary statistics such as number of eligible and valid cases, mean, standard deviation (SD), median, minimum and maximum. For categorical / qualitative data, frequencies and percentages for categories will be specified. Generally, percentages will be based on the total number of patients in the applicable analysis population as well as on the number of valid cases.

Treatment group comparisons will be based on 95% confidence intervals for the mean value or rate differences between treatment groups as well as on p-values as applicable. p-values will be interpreted descriptively as a standardized measure of effect size.

3.4 Baseline status and comparability

Demographic and baseline data for efficacy and safety measures will be summarized using descriptive statistics as noted above. Since this is a trial with randomized treatment assignment, any baseline differences between treatment groups are necessarily attributable to chance. Statistical tests for baseline comparability will therefore not be performed.

3.5 Analysis of treatment compliance

Duration of treatment will be described. As regards drug accountability data, study drug dispensation and return have been documented in the case report forms (CRFs) based on drug containers, but it was not documented systematically whether containers were full or empty. An analysis of treatment compliance beyond the analysis of treatment duration can therefore not be performed. Note that a compliance assessment as described in Section 10.4 of the study protocol was not documented in the CRFs, and according to protocol Section 8.4.3 subjects were requested to discard empty ampoules.

The number and IDs of containers dispensed and returned will be included in the subject data listings.

3.6 Analysis of efficacy

Treatment efficacy will be analyzed by performing treatment group comparisons for the efficacy outcome measures identified in Section 1.3. For outcome measures assessed at and after baseline, absolute and relative differences to the baseline value will be calculated.

For metric efficacy outcome measures, treatment group comparisons of absolute and relative change from baseline will be performed using mixed model for repeated measures (MMRM) analysis with treatment and time as categorical variables, patient as a random factor, the post-baseline assessments for the outcome of interest as the dependent variable and the baseline value as a fixed covariate. Treatment group comparisons for each post-baseline time point will be derived from these models using contrasts, and adjusted (marginal) mean values for each treatment group as well as the adjusted treatment group difference ant its 95% confidence interval will be specified.

Computations will be based on restricted maximum likelihood estimation. An unstructured covariance matrix will be used preferably. If the model does not converge, a heterogeneous Toeplitz matrix will be used instead. If this model does not converge either, a compound symmetry matrix will be used instead. If convergence cannot be achieved, treatment group comparisons of change from baseline will be performed using independent samples t-tests based on the observed means and standard deviations.

Polyposis grading and need for surgery will be analyzed as categorical variables with tabulations of frequencies and proportions. Treatment group comparisons will be performed based on U-tests (polyposis grading) and on χ^2-tests (need for surgery).

3.7 Analysis of Safety

The analysis of safety will be based on treatment emergent adverse events that are reported by the patients spontaneously or upon elicitation.

The number of events as well as the number of patients with events will be presented by MedDRA Preferred Terms and System Organ Classes for the following endpoints:

- all adverse events;
- all potentially related adverse events, i.e., events for which a causal relationship with the investigational treatment is considered to be possible, probable or very likely;
- all serious adverse events;
- serious, potentially related adverse events

Moreover, incidence densities of adverse events will be determined for each of the definitions above. The rates of potentially treatment related AEs will be compared between the study groups by computing risk ratios and their confidence intervals.

Note: Only treatment emergent AEs (commencing after exposure to study medication, i.e. during the Wash-in and Treatment phase) will be included in the AE summaries. Non- treatment emergent events (starting prior to exposure to study medication) will be included in the patient listings and not included in the above summaries.

3.8 Derived variables

Olfactometry, gustometry: since the number of stimuli presented to the patients was different between the centers, the proportion of correctly identified stimuli (number of correctly identified stimuli / number of stimuli presented * 100), not the absolute number, will be analyzed and compared between treatment groups. The documented absolute number of correctly identified stimuli will, however, be included into the subject data listings.

3.9 Handling of missing data

In the MMRM analyses to be performed on efficacy outcome measures, missing observations will be accounted for by the chosen models. Otherwise, data will be presented in an 'observed cases' analysis in which no imputation for missing values will be applied. In addition, in case of outcome measures assessed more than once during the course of the trial, analyses will be prepared in which the last valid post-baseline observation will be carried forward. In patients withdrawn from the trial for lack of efficacy or for lack of tolerability before the first post-baseline assessment, baseline values will be carried forward.

4 Data review meeting

A data review meeting (DRM) will be held as a telephone conference for assessing the observed protocol deviations and for determining the subjects' eligibility for the different analysis populations. Even though this is an open-label trial, the data to be reviewed will be presented to the meeting participants in blinded listings.

The results of the DRM will be summarized in meeting minutes to be reviewed and approved by a representative of the sponsor.

5 Software to be used

Statistical analyses will be performed using the commercially available software package IBM SPSS Statistics version 24. IBM SPSS Statistics version 24 and SigmaPlot version 14 software will be used for generating graphical displays.