1 TITLE PAGE

A randomised, open, controlled pilot study to investigate the efficacy and safety of Buparid/PARI SINUS versus Budes® Nasal Spray in the therapy of Chronic Rhinosinusitis (CRS) with polyposis nasi in adult patients

Clinical Study Report

Date of Report	21 June 2021
Version of Report	1.0
Study Phase	Pilot study
Protocol Number	12082.101
EudraCT Number	2013-002414-12
Sponsor	PARI Pharma GmbH Lochhamer Schlag 21 82166 Graefelfing (Germany)
Sponsor Contact Person	Dr. Friedrich Gruber PARI Pharma GmbH Lochhamer Schlag 21 82166 Graefelfing (Germany)
Author of Report	CLIFOPEX GmbH Bachelfeldstr. 3 84424 Isen, Germany
Datamanagement and Statistics	psy consult scientific services Am Hirschpark 1 22587 Hamburg

2 SYNOPSIS

Name of Sponsor/Company: PARI Pharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Bupari/PARI SINUS	Volume:	
Name of Active Ingredient: Bupari 1 mg / 2 ml nebuliser solution	Page:	
Title of Study: A randomised, open, controlled pilot study to investigate the efficacy and safety of Bupari/PARI SINUS versus Budes® Nasal Spray in the therapy of Chronic Rhinosinusitis (CRS) with polyposis nasi in adult patients		
Investigators: Principal Investigator: Becker, Sven, MD, PD		
Study centres: Ludwig-Maximilians-University Munich, Germany Georg-August-University, Göttingen, Germany Johannes Gutenberg-University, Mainz, Germany HNO-Centre Mangfall-Inn, Rosenheim, Germany		
Publication (reference): None		
Studied period (years): Study initiation date (first patient in): 12 May 2014 Study completion date (last patient out): 27 February 2019		Phase of development: Pilot Study
Objectives: The objective of this study is to create data for the selection of a clinically relevant primary endpoint to assess the efficacy and safety of Bupari/PARI SINUS as compared to Budes Nasal Spray in the therapy of chronic rhinosinusitis (CRS) with polyposis nasi in adult patients. Ideally, the selected parameter should allow a correlation between an objective methodology and the clinical outcome of the study patients.		
Methodology: This is a randomised, open, controlled pilot study in the therapy of CSR with polyposis nasi in adult patients.		
Number of patients planned: 20 patients are planned for this study.		
Diagnosis and main criteria for inclusion: • Patient with confirmed diagnosis of chronic rhinosinusitis (CRS), i.e. inflammation of nasal mucosa and paranasal sinus, with polyposis nasi grade I-III (according to Rasp et al. 2000). Diagnosis is based on history of symptoms (nasal obstruction, running nose, postnasal drip,		

Name of Sponsor/Company: PARI Pharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Buparid/PARI SINUS	Volume:	
Name of Active Ingredient: Buparid 1 mg / 2 ml nebuliser solution	Page:	

facial pain and hyposmia with a duration of > 3 months (according to EPOS3) and on MRT-imaging using the Lund-Mackey Score)

- Patient with a PNIF (positive nasal inspiratory flow) of > 7 l/min separated for left and right side of the nose
- Patient's written informed consent obtained prior to any screening or study-specific procedure
- Male or female, ≥ 18 years of age
- Patient is able to undergo nasal therapy without restrictions
- Capable to correctly use the PARI SINUS device (closing of the soft palate) in accordance with the package insert
- Capable of understanding the purpose and risk of the clinical trial
- Female patients with childbearing potential must have a negative urine pregnancy test prior to first IMP administration. Both women and men must agree to use a medically acceptable method of contraception throughout the IMP treatment period and for 3 months after IMP discontinuation.
- Patient is able to participate in the study according to Investigator's opinion
- Patient has completed correctly the diary during the Wash-in Phase

Test drug:

A) Buparid 1 mg/2 ml nebuliser solution (PARI Pharma GmbH); API: Budesonide

Mode of administration:

A) In patients allocated to receive Buparid, the drug was administered by a once daily inhalation (in the evening) using the PARI SINUS nebuliser. At every study visit, one inhalation cycle was monitored by the clinical trial centre personnel.

Reference drug:

B) Budes® Nasal Spray 50 µg/pump (Hexal AG); API: Budesonide

Mode of administration:

B) In patients allocated to receive Budes Nasal Spray, the drug was administered with 2 pumps per nostril twice daily (in the morning and the evening).

Criteria for evaluation:

Following screening and consenting, all participants regardless of treatment allocation received Budes Nasal Spray 50 µg (2 pumps/nostril BID) in a 2-week Wash-in Phase before starting the IMP-treatment to prevent a bias of study results due to former individualised therapies.

Name of Sponsor/Company: PARI Pharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Buparid/PARI SINUS	Volume:	
Name of Active Ingredient: Buparid 1 mg / 2 ml nebuliser solution	Page:	

After passing the Wash-in Phase and completing the diary correctly patients were randomly assigned to one of the following treatments:

Treatment arm A (Buparid/PARI SINUS, BuPS):

Buparid 1 mg/2 ml once daily for 8 weeks (2 months), resulting in a daily delivered dose of 280 µg Buparid.

Treatment arm B (Budes Nasal Spray, BuNS):

Budes Nasal Spray (50 µg/pump) 2 pumps per nostril twice daily for 8 weeks (2 months), resulting in a daily delivered dose of 400 µg.

Efficacy:

- Health-specific quality of life
- Nasal obstruction
- Inflammation of nasal mucosa and paranasal sinus
- Expansion of polyposis nasi
- Nasal inflammation
- Symptoms of rhinosinusitis
- Loss of taste/Loss of smell
- Health-specific quality of life
- Requirement of surgery
- Customer satisfaction regarding the PARI SINUS device, if applicable

Safety:

- Treatment-emergent adverse events (AEs)

Statistical methods:

An exploratory statistical analysis was performed. The treatment groups were characterized using methods of descriptive data analysis. Treatment group comparisons were based mainly on 95% confidence intervals for differences between mean values or rates.

Summary – Conclusions:

In both study treatment groups (BuPS, BuNS) there were small collectives (8 pat./6 pat.) and the number of cases declined above all in the course of the study up to week 24. The relevant efficacy parameters could be analysed and showed comparable good results for efficacy as well as for safety.

In both groups (8 BuPS/6 BuNS) a shift to lower polyp-stages was observed. BuPS-group experienced an improvement after 8-week treatment in olfaction by 33% whereas BuNS-patients showed a decline of 13%. Lund-Mackey scores improved in the BuPS-group (-3.5/-19%) and slightly worsened in the BuNS-group (+0.7/+4.8%). SNOT-22 showed a tendency of improvement in the BuPS-group (-1.0/-4%) in comparison to the BuNS-group (+2.0/+10%).

Name of Sponsor/Company: PARI Pharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Buparid/PARI SINUS	Volume:	
Name of Active Ingredient: Buparid 1 mg / 2 ml nebuliser solution	Page:	

Primary expected objective of this pilot study was, to create data for the selection of a clinically relevant primary endpoint to assess the efficacy and safety of corticosteroidal treatment using Buparid/PARI SINUS as compared to Budes Nasal Spray in the therapy of CRS with polyposis nasi in adult patients. Although the results of the efficacy parameter 'improvement in olfaction' are more pronounced ones in the BuPS-group, the data – as scheduled in ideal circumstances - do not qualify for a correlation between an objective methodology and the clinical outcome of the study patients.

Safety Results:

No new safety information was obtained during the course of the study relative to previous knowledge of budesonide. No drug-related Serious Adverse Events (SAEs), overdose, interaction, medication errors, abuse/misuse, pregnancy and/or lactation cases were reported and no life-threatening events or deaths occurred. On behalf of a patient in the wash-in phase, 'dry nasal mucosa' and for a patient under treatment with Buparid/PARI SINUS 'sinusitis' was recorded as SAE. The reason for the statements is not evident, the reported events were of mild intensity and resolved without sequels; anyhow, they do not comply with formal SAE assessment criteria. The reported nonserious AEs are well-known events for the drug and the indication respectively. Frequency, intensity and disposition to MedDRA System Organ Classes (SOC) are comparably low in both treatment groups; most recorded events are in the SOC 'Infections and infestations' (50%) and in the SOC 'Respiratory, thoracic and mediastinal disorders' (33%).

Conclusion:

Corticosteroid application by pulsating aerosols is promising in patients with CRS with polyposis nasi. It tends to improve efficacy by reaching deeper parts of the nose like the olfactory epithelium and paranasal sinuses. Further studies with larger number of patients are necessary to investigate the full potential of this treatment.

Date of report: 21 June 2021