CLINICAL TRIAL PROTOCOL

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)

Clinical Trial No.: 12082.102

EudraCT No.: 2013-002421-30

Protocol Amendment 1

Protocol Version 2

Date: 17 July 2015

Sponsor: PARI Pharma GmbH
Lochhamer Schlag 21
82166 Graefelfing
Germany

Signature Page 3

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)

Investigator's Signature:

I have read the protocol and the protocol appendices. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorisation by PARI Pharma GmbH in the form of a protocol amendment.

The Investigator is responsible for performing the study in accordance with this protocol, Directive 2001/20/EC, UK, FDA regulations, and any applicable local regulatory regulations where applicable, the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP), and for collecting, recording, and reporting the data accurately and properly. Agreement of the Investigator to conduct and administer this study in accordance with the protocol will be documented in a separate study agreement with the Sponsor, and other forms as required by Competent Authorities in the country where the study centre is located.

The Investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study, and must ensure that fully functional resuscitation equipment and personnel trained in its proper use are immediately available in case of a medical emergency. The Investigator must be familiar with the background to and requirements of the study and with the properties of the study drug as described in the Investigator's Brochure, summary of product characteristics (SmPC) or package insert.

The Principal Investigator at each centre has the overall responsibility for the conduct and administration of the study at that centre, and for contacts with study centre management, the Ethics Committee (EC), and with the Competent Authority (CA).

_____ _____

Date [Signature]

2. PROTOCOL SYNOPSIS

Study 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)
Sponsor:	PARI Pharma GmbH Lochhamer Schlag 21 82166 Graefelfing Germany
Protocol Number:	12082.102
EudraCT Number:	2013-002421-30
Product:	Buparid 1 mg/2 ml nebuliser solution
Study Phase:	Pilot study
Protocol Amendment 1 Date:	17 July 2015
Original Protocol Date:	13 December 2013
Study Centres/Countries:	3 centres in Germany: Georg-August-University Göttingen; Ludwig-Maximilians-University Munich Johannes Gutenberg-Universität Mainz
Planned Study Period (First Patient In – Last Patient Out):	Start: March 2015 (FPI) Enrolment period: 12 months Duration of therapy: 2 months Duration of Follow-up: 10 months Duration of study: 24 months (LPO: March 2017)
Planned number of subjects:	A total of approximately 20 (2 x 10) evaluable patients are assumed to be sufficient to create enough data for the selection of an appropriate primary endpoint for a confirmatory study intending to demonstrate therapeutic benefit and to evaluate the adverse effect profile of Buparid/PARI SINUS in comparison to Budes® Nasal Spray.

Objective:	The objective of this study is to analyse whether Buparid/PARI SINUS has a higher potential to avoid or postpone sinus surgery in adult patients with CRS than Standard of Care therapy with Budes® Nasal Spray. The results of this study are expected to provide estimates for a proper sample size calculation to conduct a pivotal study.
Study Design:	This is a randomised, open, controlled pilot study in the therapy of CSR in adult patients.
Inclusion Criteria:	1. Patient with confirmed diagnosis of chronic rhinosinusitis (CRS), i.e. inflammation of nasal mucosa and paranasal sinus. Diagnosis is based on history of symptoms (nasal obstruction, running nose, postnasal drip, facial pain and hyposmia with a duration of > 3 months (according to EPOS3) and on MRT-imaging (Lund-Mackey Score [Score: 0-24]) 2. Patient without alternative other than sinus surgery 3. Patient's written informed consent obtained prior to any screening or study-specific procedure 4. Male or female, ≥ 18 years of age 5. Patient is able to undergo nasal therapy without restrictions 6. Capable to correctly use the PARI SINUS device (closing of the soft palate) in accordance with the package insert 7. Capable of understanding the purpose and risk of the clinical trial 8. 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. 9. Patient is able to participate in the study according to Investigator's opinion
Exclusion Criteria:	1. Patients with cystic fibrosis 2. Patients with polyposis nasi grade I-IV (according to Rasp et al. 2000) 3. Patients with prior FESS (Functional Endosopic Sinus Surgery) 4. Pregnant or breastfeeding women

	5. Any active invasive bacterial, viral or fungal infection within one week prior to first investigational medicinal product (IMP) administration 6. No clinically relevant abnormal parameters of vital signs, blood biochemistry or renal/hepatic function 7. Unlikely to comply with visits, inhalation procedures or other measurements scheduled in the protocol 8. Receipt of an investigational drug as part of a clinical trial within 4 weeks prior to first administration of IMP 9. Any co-existing medical condition that in the Investigator's judgement will substantially increase the risk associated with the patient's participation in the clinical trial 10. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary procedures 11. Drug or alcohol abuse 12. End-stage malignancies 13. Known hypersensitivity to Budesonide 14. Patients with oral steroid therapy within the last 3 months 15. Patients needing > 1 mg/day Budesonide (or steroidal equivalent) for therapy of asthma 16. Patients on therapy with leukotriene-receptor antagonists, decongestants, antihistamines or antibiotics 17. Patients with frequent epistaxis (> 1 episode per week)
Investigational Medical Product:	A) Buparid 1 mg/2 ml nebuliser solution (PARI Pharma GmbH); API: Budesonide B) Budes® Nasal Spray 50 µg/pump (Hexal AG); API: Budesonide
Mode of Administration/Dosing Schedule:	A) In patients allocated to receive Buparid, the drug will be administered by a once daily inhalation (in the evening) using the PARI SINUS nebuliser. At every study visit, one inhalation cycle will be monitored by the clinical trial centre personnel. B) In patients allocated to receive Budes® Nasal Spray, the drug will be administered with 2 pumps per nostril twice daily (in the morning and the evening).
Treatment Regimen:	Following screening and consenting, all participants regardless of

	treatment allocation will receive Budes® Nasal Spray (2 pumps/nostril BID) in a 1-week Wash-in Phase before starting the IMP-treatment to prevent a bias of study results due to former individualised therapies. After passing the Wash-in Phase patients will be randomly assigned to one of the following treatments: *Treatment arm A (Buparid/PARI SINUS):* 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):* 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. In case a re-decision for sinus surgery is made whilst the patient is still on control treatment, a switch to Buparid/PARI SINUS is allowed as rescue therapy. After completion of the treatment period, patients will be followed-up for necessity of sinus surgery after 3 and 6 months via a questionnaire. A final assessment including a visit at the clinic including the investigation of patients' clinical signs will occur 12 months after randomisation.
Endpoints:	***Efficacy:*** • Health-related quality of life • Nasal obstruction • Inflammation of nasal mucosa and paranasal sinus • Clinical parameters • Symptoms of rhinosinusitis • Loss of taste/Loss of smell • Avoidance or postponing of sinus surgery • Customer satisfaction regarding the PARI SINUS device, if applicable ***Safety (during the whole study period):*** • Treatment-emergent adverse events (AEs)
Assessment of Efficacy:	Health-related quality of life (at Visit 0, 1, 2, 3, 4, 5 and 6): • SNOT 20-GAV (Sino-Nasal Outcome Test 20-German Adapted Version) Nasal obstruction (at Visit 0, 1, 2 and 3): • Rhinonanometry

	Inflammation of the nasal mucosa and paranasal sinus (at Visit 1 and Visit 3):
	• Magnetic Resonance Imaging
	  o Thickness of mucosa
	  o Lund-Mackay-Score
	Clinical parameters (at Visit 0, 3 and 6):
	• EAS (Endoscopic Appearance Score)
	Symptoms of rhinosinusitis (at Visit 0, 1, 2, 3, 4, 5 and 6):
	• VAS (Visual Analogue Scale)
	Loss of taste/Loss of smell (at Visit 0, 1, 3 and 6):
	• Gustometry/Olfactometry
	Avoidance or postponing of sinus surgery (at Visit 3, 4, 5 and 6):
	• Time to sinus surgery (as calculated from randomization onwards)

Assessment of Safety:	The following safety parameters will be assessed at each clinical visit: • Treatment-emergent adverse events (AEs)
Statistical Considerations:	An exploratory statistical analysis will be performed. The treatment groups will be characterized using methods of descriptive data analysis. Treatment group comparisons will be based mainly on 95% confidence intervals for differences between mean values or rates.

Study Visit Schedule

Assessment	Visit 0 Week -1	Visit 1 Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 24	Visit 6 Week 48
Informed consent	X						
In-/Exclusion criteria	X						
Urine pregnancy test[1]	X						
Demographics[2]	X						
Medical history[3]	X						
IMP administration	X[4]	X	X				
Inhalation compliance[5]			X	X			
Health-related Quality of Life	X	X	X	X	X	X	X
Nasal obstruction	X	X	X	X			
Inflammation of nasal mucosa and paranasal sinus using MRI		X		X			
Endoscopic Appearance Score	X			X			X
Symptoms of rhinosinusitis	X	X	X	X	X	X	X
Loss of taste/Loss of smell	X	X		X			X
Requirement of surgery	X			X	X	X	X
Customer satisfaction[6]					X	(X)	
Concomitant treatment[7]	X	X	X	X	X	X	X
Adverse Events (AEs)	X[8]	X	X	X	X	X	X

[1] Only in women of childbearing potential
[2] Year of birth, gender, race, height, weight, nicotine and alcohol consumption
[3] Underlying condition, antibacterial/-viral/-fungal therapy
[4] Budes® Nasal Spray for Wash-in
[5] Collection of used Buparid ampoules/Budes® Nasal Sprays
[6] Only in patients randomized to Buparid/PARI SINUS treatment
[7] Name of drug, dosage, duration
[8] Baseline signs and symptoms
(X) If not performed on previous visit

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ADR	Adverse Drug Reaction
API	Active Product Ingredient
AR	Adverse Reaction
BFS	Blow/Fill/Seal
BID	Bis In Die; twice daily
CA	Competent Authority
CRF	Case Report Form
CRS	Chronic Rhinosinusitis
CT	Computer Tomography
CTC	Common Toxicity Criteria
CYP	Cytochrome P450
DTPA	Diethylene Triamine Pentaacetic Acid
EC	Ethics Committee
ECG	Electrocardiogram
EOS	End Of Study
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
FL	Frontal Sinus Left
FPI	First Patient In
FR	Frontal Sinus Right
GCP	Good Clinical Practice
hPa	Hecto Pascal
Hz	Hertz
ICH	International Conference on Harmonization
ID	Identification
IMP	Investigational Medicinal Product (study drug)
LPO	Last Patient Out
mbar	Millibar
MeDRA	Medical Dictionary for Regulatory Activities
ML	Maxillary Sinus Left
MMAD	Mass Median Aerodynamic Diameter
MR	Maxillary Sinus Right
MRI	Magnetic Resonance Imaging
MRT	Magnetic Resonance Tomography
N	Number
PNIF	Positive Nasal Inspiratory Flow
PP	Per Protocol Analysis
QD	Quorum Die; once daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation

SmPC	Summary of Product Characteristics
SNOT 20-GAV	Sino-Nasal Outcome Test 20 – German Adapted Version
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
V	Volt
VAS	Visual Analogue Scale
WHO	World Health Organization

5. INTRODUCTION

5.1 Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis (CRS) is one of the most commonly diagnosed chronic illnesses affecting approx. 10-15% of the European population (van Cauwenberge 2000; Fokkens 2007). It is the common understanding that inflammation of the nasal mucosa (i.e., rhinitis) due to bacterial or viral infections, allergies, or exposure to inhaled irritants leads to acute sinusitis. Chronic inflammation of the nasal mucosa results in mucosal swelling, increased mucus secretion, loss of cilia, airway obstruction and blocked sinus drainage. Under these conditions, bacteria and viruses that are normally removed from the nasal cavity and sinuses by drainage of secretions may proliferate. This blockage of mucus drainage from the sinuses and reduced ventilation creates an environment for chronic rhinosinusitis (Clement 1997, Baraniuk 2005). Impaired mucociliary clearance in patients with primary ciliary dyskinesia may also cause chronic sinusitis (Armengot 1994, Min 1995).

CRS is a common problem that results in significant impairment of quality of life. Associated symptoms drive a patient to seek medical opinion. Although the definition of chronic rhinosiusitis is based on the occurrence and duration of symptoms, many clinicians use computer tomography (CT) scans to confirm the presence of disease, assess severity, and aid management decisions. It is often assumed that patients' symptoms correlate to "objective" scores of disease severity. However, the relationship between radiologic findings and symptoms at presentation in sinusitis remains controversial. The predictive value of radiologic scores in terms of symptomatic improvement after surgical intervention is also unknown. If radiologic finding do not correlate with either pre-treatment symptoms or the outcome of treatment, it may be wrong to base treatment decisions on findings that do not reflect the patient's symptom load (Hopkins 2007).

It is a common practice to use systemic or topical corticosteroids as the first therapeutic choice, followed by surgery for resistant or recurrent cases. There is good evidence, in the form randomized controlled trials, to support the use of topical nasal corticosteroids. Short courses of systemic corticosteroids are also widely used in clinical practice to provide rapid relief of symptoms, followed by the use of long-term topical corticosteroids.

Various outcome measures have been used to analyse the results of intervention in this patient population (Piccirillo 1995, Piccirillo 2002). Most of these are questionnaire-based visual analogue scores of symptoms and quality of life. Visualization may be performed by means of nasendoscopy or imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI); these approaches offer more objective methods of measuring treatment response. Many previous studies have shown a poor relationship between symptoms and objective measurement of pathology (Bhattacharyya 1997, Stewart 1999, Wabnitz 2005).

Due to the fact that the nose is an efficient filter for inhaled aerosol particles and the paranasal sinuses being virtually not ventilated there is limited success in the topical drug delivery to the nose and the paranasal sinuses when using nasal sprays. Despite the fact that the sinuses are poorly-ventilated hollow organs, *in vivo* and *in vitro* studies have shown that nebulized rugs can be deposited into the paranasal sinuses, although at very low concentrations (Sato 1981; Möller 2008). Therefore, the primary option of treatment of CRS is surgery, often in

combination with topical and systemic medical treatment. An efficient topical therapy may allow treating upper respiratory diseases more effectively, prevent sinus surgery or at least extend the time span for sinus surgery. This hypothesis is supported by clinical data upon nasal administration of Dornase alpha (Pulmozyme) vial pulsating aerosol delivery (PARI SINUS) in cystic fibrosis patients (Mainz 2008).

The objective of this study is to analyse whether Budesonide PARI/SINUS has a higher potential to avoid or postpone sinus surgery in adult patients with CRS than Standard of Care therapy with Budes® Nasal Spray. The results of this study are expected to provide estimates for a proper sample size calculation to conduct a pivotal study.

5.2 Budesonide

It is accepted that inflammation is the key pathological process of CRS. Budesonide is a glucocorticosteroid with strong local corticosteroidal effect and exerts anti-inflammatory, anti-allergic, anti-exudative and anti-oedematous activity, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids. Due to these characteristics the following effects can be achieved:

- Inhibition of the formation, retention and release of mediators from mast cells, basophils and macrophages
- Reduction of the hyper-responsiveness of the epithelia to exogenous stimuli
- Reduction of the cholinergic stimuli, thus resulting in a decrease of secret production
- Proofing of the epithelial and endothelial membrane
- Reduction of inflammatory symptoms (oedema, cellular infiltration)

The anti-inflammatory actions, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably the most important.

5.3 PARI SINUS – Pulsating Aerosol Delivery System

A pulsating aerosol is generated using the PARI Sinus system (PARI GmbH, Starnberg, Germany). It is based on a PARI BOY N aerosol drug delivery device. The compressor has an integrated pressure wave generator driven by the same motor. The pressure wave has a 45 Hz frequency with amplitude of 25 mbar. It is attached via a tubing connector to the vent opening of a PARI LC SPRINT Junior jet nebulizer in order to superimpose the pressure wave on the aerosol flow. The mass median aerodynamic diameter (MMAD) of the aerosol generated by the PARI LC SPRINT Junior jet nebulizer is 3.2 µm with a geometric standard deviation of 2.6. The rate of mass output is 0.2 ml/min. For aerosol delivery to the nose the nebulizer is coupled to the right nostril and the left nostril vial a flow resistor to output tubing. During delivery the subject closes his soft palate, which directs the aerosol to the output nostril and prevents aerosol penetration to the lung.

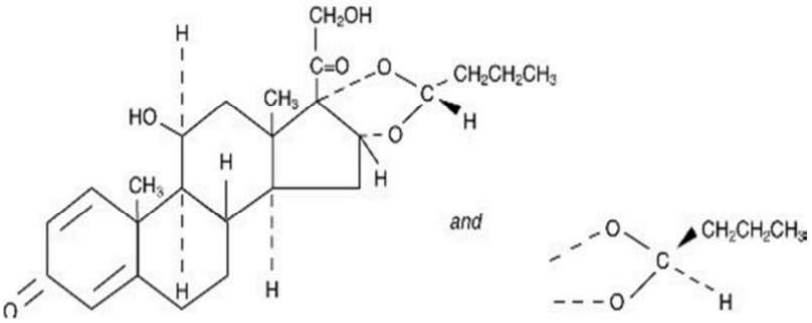
6. BACKGROUND INFORMATION

6.1 Name and Description of Investigational Medicinal Product

Bupard (budesonide) is a potent, non-halogenated glucocorticosteroid which, when administered by inhalation, possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids. Bupard has negligible mineralocorticoid activity. Bupard belongs to the Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: RO3B A02. Chemically, Bupard is (11β,16α)-16,17- (Butylidenebis(oxy))-11,21-dihydroxypregna-1,4-diene-3,20-dione (CAS number 51333-22-3). Budesonide is present as the two epimers designated (22R) and (22S) which do not interconvert.

The empirical formula is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. The structural formula is depicted in Figure 2 below.

Figure 2 Chemical Structure of Budesonide -22R and -22S epimer



Bupard-(22R), Bupard-(22S)

Bupard is a sterile suspension obtained using the known excipients disodium edetate, sodium chloride, polysorbate 80 (Tween 80), citric acid anhydrous, sodium citrate and water for injections. The suspension is white and homogeneous with a pH between 4.0 to 5.0 and a relative density of 1.005 g/ml. Bupard is available as 0.125mg/ml, 0.250mg/ml and 0.5mg/ml strengths.

Bupard is contained in unit dose containers of low density polyethylene without additives, slightly opaque and thermally sealed, obtained from polyethylene granules by Blow/Fill/Seal (BFS) technology. The nominal volume of these unit dose containers is 2.00 ml. 20 labelled unit dose containers, divided in 4 strips of 5 containers, are contained in PET/Al/PE pouches (1 strip in each pouch) and then in a suitable lithographed box, together with the leaflet.

6.2 Findings from Non-clinical and Clinical Studies

6.2.1 Non-clinical Studies

The active ingredient budesonide is widely used in a number of dosage forms including: inhalational powder, inhalational suspension, nasal suspension, rectal foam, and oral capsules. The primary pharmacology, toxicology, clinical pharmacology and clinical efficacy of budesonide has been established since 1980 and the pre-clinical and clinical data and has been reviewed by multiple competent agencies.

6.2.1.1 Sino-nasal Deposition of inhalable drugs using the PARI SINUS nebuliser – Technical Data

PARI SINUS compressor

- 230 V/50 Hz
- Pressure 1,400 hPa
- Flow 6 l/min
- Pressure amplitude of bolus 211 hPa
- Frequency of bolus 44.5 Hz

PARI LC-SPRINT SINUS nebuliser

- MMD 3.6 µm
- Jetflow 4.6 l/min

The nebuliser output rate is approx. 200 mg/min, ie. within 8 min (= effective therapy duration time without breaks) 1.600 mg aerosol are delivered to the patient. This corresponds to approx. 1.6 ml inhalation medium.

6.2.1.2 Pharmacokinetic Properties

Absorption
In adults the systemic availability of budesonide following administration of budesonide nebuliser suspension via a jet nebuliser is approximately 15% of the nominal dose and 40% to 70% of the dose delivered to the patients. A minor fraction of the systemically available drug comes from swallowed drug. The maximal plasma concentration, occurring about 10 to 30 min after start of nebulisation is approximately 4 nmol/l after a single dose of 2 mg.

Distribution
Budesonide has a volume of distribution of approximately 3 l/kg. Plasma protein binding averages 85 - 90%.

Biotransformation
Budesonide undergoes an extensive degree (≈ 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6ß-hydroxybudesonide and 16a-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

Elimination
The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 l/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours.

6.2.1.3 Toxicology

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclomethasone dipropionate, fluocinolone acetonide).

Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe or similar to those observed after administration of other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class-effect.

Available clinical experience shows that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However these animal experimental results do not appear to be relevant in humans at the recommended doses.

Animal studies have also identified an involvement of excess prenatal glucocorticosteroids in increased risk for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

6.2.2 Clinical Studies

Not applicable. This is the first study with Buparid/PARI Sinus in this indication.

6.3 Known and Potential Risks and Benefits to Human Patients

Potential Risks:

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis and in patients with fungal or viral infections in the airways.

During transfer from oral therapy to Buparid, a generally lower systemic corticosteroid action will be experienced, which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these

conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk of impaired adrenal function. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery.

Systemic effects may occur with any inhaled corticosteroids, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary.

Adverse drug reactions in Table 6.3-1 are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).

The likelihood of adverse events may be related to the age, renal function and condition of the patient.

Table 6.3-1: Adverse Drug Reactions

Adverse Reactions	Frequency category
Infections and infestations	
Oropharyngeal candidiasis	Common
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Hoarseness	Common
Throat irritation	Common
Bronchospasm	Rare
Dysphonia	Rare
Immune system disorders	
Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction	Rare
Endocrine disorders	
Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation	Rare
Psychiatric disorders	
Psychomotor hyperactivity	Rare
Sleep disorders	Rare
Anxiety	Rare
Depression	Rare
Aggression	Rare
Behaviour changes (predominantly in children)	Rare
Skin and subcutaneous tissue disorders	
Bruising	Rare
Eye disorders	
Glaucoma	Not known
Cataract	Not known

Potential Benefits:

The conception of the SINUS technology is based on a more efficient drug deposition as compared to nasal spray delivery. Because of pulsation the drug is pressed through the congested ostia and allows penetration to the desired locus of action. The demonstrated residence time of pulsating aerosols should allow increasing the convenience of therapy by reduction of a twice-daily to a once-daily application.

Given the correctness of these assumptions, the pulsating aerosol therapy might prevent or at least postpone a surgical intervention.

6.4 Selection of Drugs and Doses

Table 6.4-1: Selection of Drugs and Doses

Drug	Delivered Dose/ Treatment (µg)	QD (µg)	Daily Dose (µg)	BID (µg)	Daily Dose (µg)
Buparid (1 mg/2 ml)	280	1 x 280	280	2 x 280	560
Pulmicort Topinasal 64 µg	64 / Pump	2 pumps/nostril = 4 x 64	256	2 x 1 pump/nostril = 4 x 64	256
Budes® Nasal Spray 50 µg	50 / Pump	4 pumps/nostril = 8 x 50	400	2 x 2 pumps/nostril = 8 x 50	400

The rationale for the selection of a once-daily treatment of Buparid/SINUS and a twice-daily treatment with Budes® Nasal Spray is that despite the lower daily dose administered via the former system a sufficient drug amount is deposited via a more efficient delivery system, resulting in at least comparable efficacy.

There are two mayor differences between the SINUS nebulizer and nasal sprays:

First, the droplet size is 3 µm for the SINUS and 50 µm for nasal pump sprays. As the nose is a very efficient particle filter, especially for particles larger than 10 µm, the aerosol mist of a nasal spray deposits at 100% in the anterior nose, mainly at the nasal vestibule and at the inferior turbinates. Very small droplets, as produced by the SINUS, can penetrate into the posterior regions of the nose and are only partly deposited there.

The second major difference is that the nasal spray is applied during one inhalation manoeuvre to the nose, while the SINUS aerosol is applied with a pulsating air flow. The flow fluctuations at 45 Hz cause a ventilation of the sinus cavities in the nose, as shown in Figure 6.4-1 below. The small droplets generated by the SINUS are capable to follow the induced airflow to the paranasal sinuses and deposit there.

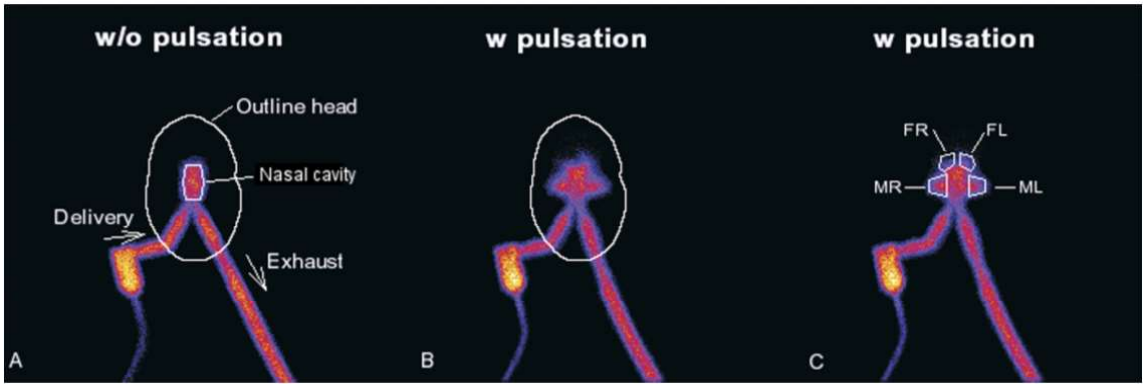


Figure 6.4-1: Anterior nasal 81mKr-gas gamma imaging without (w/o, A) and with (w, B and C) pulsating airflow. The nebulizer, coupled to the right nostril, and the exhaust tubing, coupled to the left nostril, is shown. Regions of interest of the nasal cavity (A) and of the right and left maxillary and frontal sinuses (MR, FR, FL, and ML) are shown (C) [from Möller et al. 2010].

These differences in droplet size and air flow result in very different deposition patterns of nasal sprays versus SINUS as illustrated in Figure 6.4-2. While nasal sprays deposit mainly at the anterior nose, the SINUS delivers also aerosol to the upper posterior regions of the nose as well as to the maxillary, sphenoid and ethmoid sinuses. These different deposition patterns also result in different clearance times of the deposited particles from the nose.

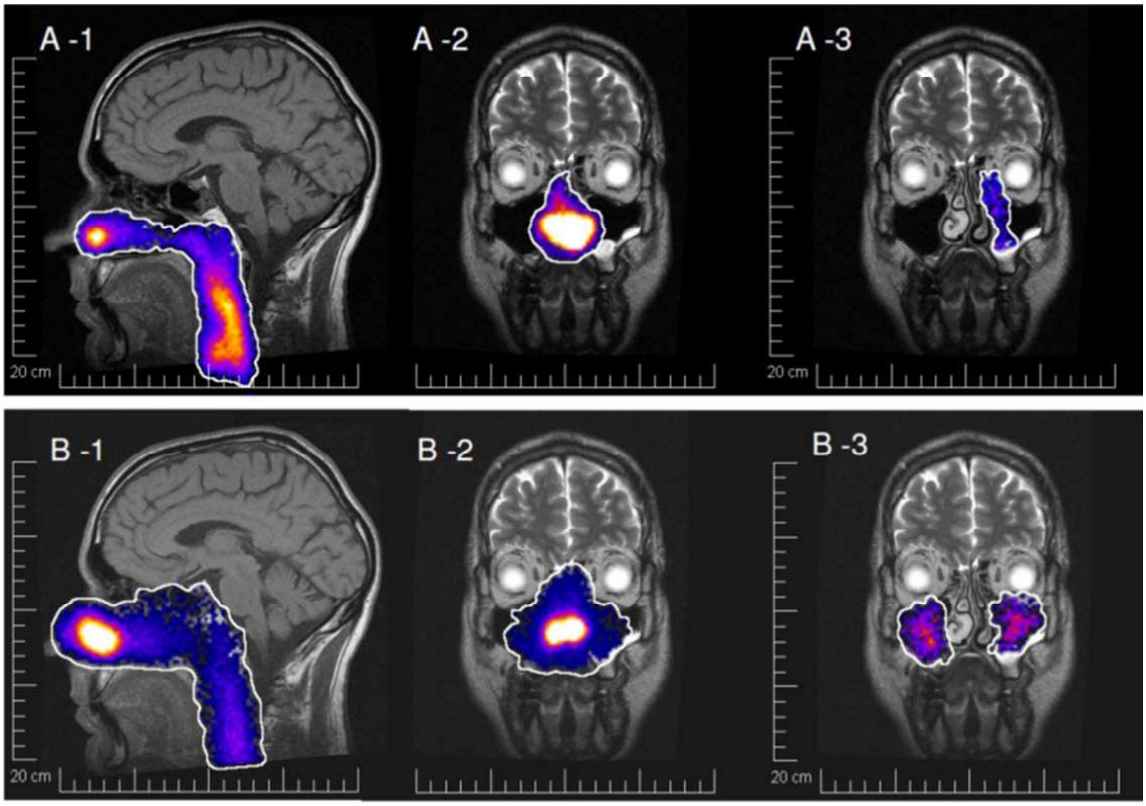


Figure 6.4-2: 99mTc-DTPA activity distribution image of a pump spray (A) vs. pulsating aerosol delivery (B) in lateral and anterior view without a nasal shield (Fig. 1, 2) and with a nasal shield (from Möller et al 2009).

The 50% nasal retention was five times faster for nasal pump sprays than for pulsating aerosol in healthy volunteers (Table 6.4-1).

Table 6.4-1: Results of retention using nasal pump sprays and pulsation aerosol delivery (from Möller et al. 2010).

	Nasal Pump Spray	Pulsating Aerosol
50% Nasal retention	14 ± 3.4 min	72 ± 30 min
24 h Nasal retention	2.4 ± 1.8 %	7.6 ± 1.3 %
6 h cumulative dose	0.33 ± 0.11 h	1.98 ± 0.23 h

The prolonged residence time of pulsating aerosols might allow a once daily treatment (Figure 6.4-3).

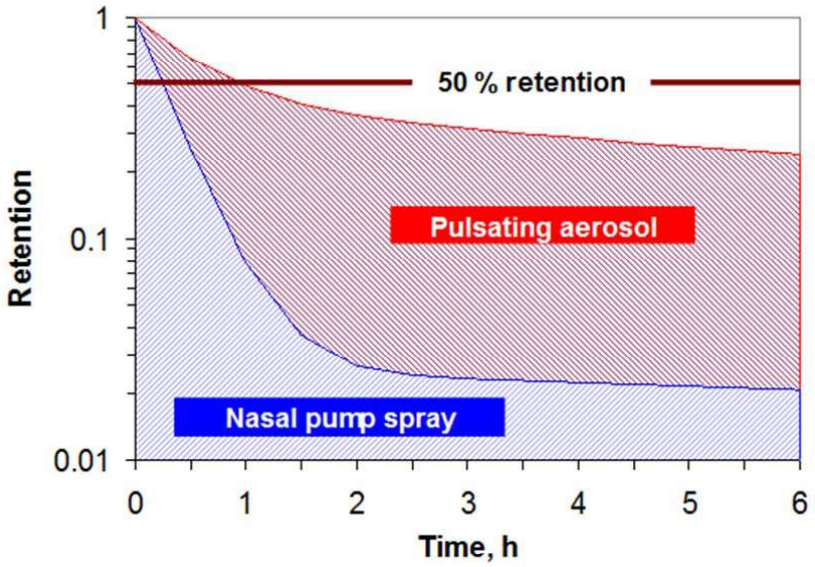


Figure 6.4-3: ^{99m}Tc-DTPA nasal retention during six hours in a volunteer after delivery using a nasal pump spray or the pulsation aerosol device (from Möller et al. 2010).

6.5 Population Studied

Adult patients with confirmed diagnosis of chronic rhinosinusitis (CRS), i.e. inflammation of nasal mucosa and paranasal sinus.

7. TRIAL OBJECTIVES AND PURPOSE

The objective of this study is to analyse whether Budesonide PARI/SINUS has a higher potential to avoid or postpone sinus surgery in adult patients with CRS than Standard of Care therapy with Budes® Nasal Spray. The results of this study are expected to provide estimates for a proper sample size calculation to conduct a pivotal study.

8. TRIAL DESIGN

This is a randomised, open, controlled pilot study in the therapy of CSR in adult patients.

The design of this pilot study was driven by the aim to figure out parameters which allow a correlation of objectively measurable parameters with methods implying a low burden for the patient with the subjective patient outcome records. Apart from this, the overall purpose of the investigational treatment is to prolong the time to or even prevent unavoidable sinus surgery. Therefore, the possibility of a cross-over from reference therapy to investigational therapy in case of treatment failure is integrated.

As this is a pilot study including only a low patient number results will only be analysed descriptively and a positive or negative outcome cannot be generalized. This will need to be demonstrated in a subsequent confirmatory study.

8.1 Endpoints

Efficacy:

- Avoidance or postponing of sinus surgery
- Inflammation of nasal mucosa and paranasal sinus
- Nasal obstruction
- Health-related quality of life
- Symptoms of rhinosinusitis
- Loss of taste/Loss of smell
- Clinical parameters

Safety (during the whole study period):

- Treatment-emergent adverse events (AEs)

8.2 Trial Design

This is a randomised, open, controlled pilot study to investigate the efficiency of drug delivery using the PARI SINUS device versus nasal spray in the therapy of CSR in adult patients. The study will be conducted in three centres in Germany. Patients will be allocated to receive either 1 mg/2 ml Buparid therapy once daily or the recommended twice daily doses of Budes® Nasal Spray. Patients will be monitored at regular intervals during 12 months for efficacy parameters and for all safety evaluations.

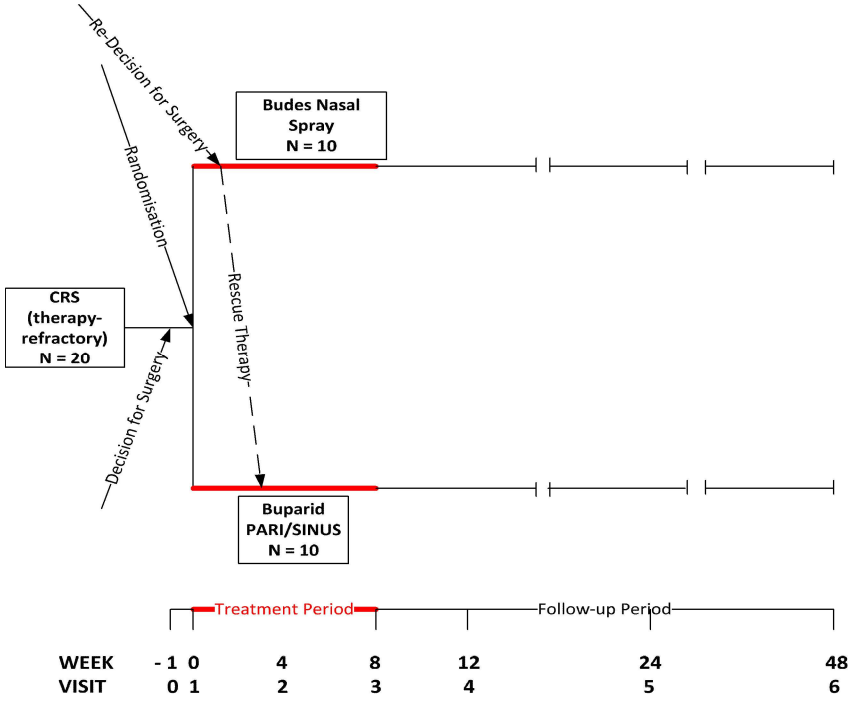
8.2.1 Trial Overview

Study Visit Schedule

Assessment	Visit 0 Week -1	Visit 1 Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 24	Visit 6 Week 48
Informed consent	X						
In-/Exclusion criteria	X						
Urine pregnancy test[1]	X						
Demographics[2]	X						
Medical history[3]	X						
IMP administration	X[4]	X	X				
Inhalation compliance[5]			X	X			
Health-related Quality of Life	X	X	X	X	X	X	X
Nasal obstruction	X	X	X	X			
Inflammation of nasal mucosa and paranasal sinus using MRI		X		X			
Endoscopic Appearance Score	X			X			X
Symptoms of rhinosinusitis	X	X	X	X	X	X	X
Loss of taste/Loss of smell	X	X		X			X
Requirement of surgery	X			X	X	X	X
Customer satisfaction[6]					X	(X)	
Concomitant treatment[7]	X	X	X	X	X	X	X
Adverse Events (AEs)	X[8]	X	X	X	X	X	X

[1] Only in women of childbearing potential
[2] Year of birth, gender, race, height, weight, nicotine and alcohol consumption
[3] Underlying condition, antibacterial/-viral/-fungal therapy
[4] Budes® Nasal Spray for Wash-in
[5] Collection of used Buparid ampoules/Budes® Nasal Sprays
[6] Only in patients randomized to Buparid/PARI SINUS treatment
[7] Name of drug, dosage, duration
[8] Baseline signs and symptoms
(X) If not performed on previous visit

8.2.2 Study Flowchart



8.3 Randomisation and Stratification

Patients will be screened by the Investigators to assess eligibility for entry into the study. A master log will be maintained for all screened patients. When a patient arrives in the clinic for the Visit 0, the Investigator will confirm that the patient meets all eligibility criteria.

After clinical inclusion and exclusion criteria have been fully evaluated and the Wash-in phase has been completed, twenty patients will be prospectively randomized in a 1:1-ratio among the two treatments and control groups by block randomization. Randomization will be performed by an electronically generated algorithm. The randomization code of each patient will be provided to the Principal Investigator via closed and blinded envelops. Each patient will be assigned a number as part of the randomization process. The number assigned to a patient will become that patient's unique treatment number throughout the study and cannot be re-assigned to another patient.

No treatment will be assigned to a patient before it has been ascertained that the patient has met all inclusion and no exclusion criteria and that the patient or her/his legal representative has given written informed consent.

If the informed consent from the patient is obtained but the patient does not fulfil the criteria to participate in the study, the patient will not receive a randomisation number; however, data collected at screening may be recorded in the patient's source data and on the subject identification log.

A stratification into subgroups is not planned due to the limited patient number of this pilot study.

8.3.1 Blinding

Not applicable; this is an open-labelled study.

8.4 Investigational Medicinal Product Treatment, Dosage and Administration

8.4.1 Formulation of Buparid

Buparid is a sterile suspension obtained using the known excipients disodium edetate, sodium chloride, polysorbate 80 (Tween 80), citric acid anhydrous, sodium citrate and water for injections. The suspension is white and homogeneous with a pH between 4.0 to 5.0 and a relative density of 1.005 g/ml. Buparid is available as 0.125 mg/ml, 0.250 mg/ml and 0.5 mg/ml strengths.

Buparid is contained in unit dose containers of low density polyethylene without additives, slightly opaque and thermally sealed, obtained from polyethylene granules by Blow/Fill/Seal (BFS) technology. The nominal volume of these unit dose containers is 2.00 ml. 20 labelled unit dose containers, divided in 4 strips of 5 containers, are contained in PET/Al/PE pouches (1 strip in each pouch) and then in a suitable lithographed box, together with the leaflet.

The IMP (Buparid/PARI SINUS and Budes® Nasal Spray 50µg/pump) will be supplied by:

PARI Pharma GmbH
Lochhamer Schlag 21
82166 Graefelfing
Germany

8.4.2 Treatment and Dosage

Following screening and consenting, all participants regardless of treatment allocation will receive Budes® Nasal Spray 50 µg (2 pumps/nostril BID) in a 1-week Wash-in Phase before starting the IMP-treatment to prevent a bias of study results due to former individualised therapies.

After passing the Wash-in Phase patients will be randomly assigned to one of the following treatments:

Treatment arm A (Buparid/PARI SINUS):

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):

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.

8.4.3 Administration

All IMP inhalation with the PARI SINUS nebuliser during the scheduled visits MUST be self-administered by the patient under trial centre personnel supervision.

Instructions for administration should be followed as described on the inside leaflet of the medication package.

Instructions for using Buparid ampoules

1. Break off the required number of ampoule(s) from the strip. Leave the rest in the foil envelope.
2. Shake the ampoule(s) gently.
3. Hold upright. Open the ampoule by twisting off the top of the ampoule(s).
4. Pour the quantity of medication prescribed by your doctor into the medication funnel.
5. Throw away the empty ampoule(s). Close the cap of the nebuliser.
6. Connect the face mask or mouthpiece to the nebuliser according to the nebuliser instructions.
7. Connect the nebuliser handset to the compressor.
8. Switch on the compressor. Using the face mask or mouthpiece, breathe in the mist calmly and deeply while sitting or standing in an upright position. If you are using a face mask, make sure that the mask fits tightly.
9. You will know when you have inhaled all of the medicine because the fine mist will stop coming out of your mask or mouthpiece.
10. How long it takes to nebulise all the medicine depends on the type of equipment you use. It will also depend on the amount of medicine you use.
11. Several drops of medication will remain in the nebuliser after inhalation.
12. Rinse your mouth with water. Spit out the water. Do not swallow it. If you have used a face mask, wash your face as well.
13. After each use, you must wash the nebuliser medication reservoir and mouthpiece (or face mask).

8.5 Investigational Medicinal Product Packaging, Labelling and Storage

8.5.1 Packaging

8.5.1.1 Buparid

Buparid will be provided as 20 labelled unit dose ampoules (1 mg/2 ml each), divided in 4 strips of 5 ampoules in pouches (1 strip in each pouch) and then in an outer packaging box.

Pouches with 5 ampoules of IMP

- PARI Pharma GmbH, Lochhamer Schlag 21, 82166 Graefelfing, Germany, Tel.: +49 (0)89 742846-10
- Batch: XXXXX: Protocol-No. 12082.102
- Site: 1 or 2, PI: XXXXX
- Subject No.: XX
- Dose: 1 mg/2 ml
- Route of administration: Inhalation
- FOR CLINICAL TRIAL USE ONLY

Outer Packaging Containing 20 IMP ampoules

- Sponsor: PARI Pharma GmbH, Lochhamer Schlag 21, 82166 Graefelfing, Germany, Tel.: +49 (0)89 742846-10
- 20 ampoules of investigational medical product
- Batch: XXXXX: Protocol-No. 12082.102
- Site: 1 or 2, PI: XXXXX
- Subject No.: XX
- Box No.: XX
- Route of administration: Inhalation
- Do not store above 30°C, do not freeze, protect from light
- Expiry Date: dd/mm/yyyy
- “Keep out of reach of children”
- FOR CLINICAL TRIAL USE ONLY

8.5.1.2 Budes® Nasal Spray

Budes® Nasal Spray 50 µg/pump will be provided in packages of 1 nasal spray á 10 ml suspension for 200 single doses.

Budes® Nasal Spray

- PARI Pharma GmbH, Lochhamer Schlag 21, 82166 Graefelfing, Germany, Tel.: +49 (0)89 742846-10
- Batch: XXXXX: Protocol-No. 12082.102
- Site: 1 or 2, PI: XXXXX
- Subject No.: XX

Outer Packaging Containing 1 Nasal Spray

- Sponsor: PARI Pharma GmbH, Lochhamer Schlag 21, 82166 Graefelfing, Germany, Tel.: +49 (0)89 742846-10
- 1 Nasal Spray
- Batch: XXXXX: Protocol-No. 12082.102
- Site: 1 or 2, PI: XXXXX
- Subject No.: XX
- Box No.: XX
- Route of administration: Nasal spray
- Do not store above 25°C, do not freeze
- Expiry Date: dd/mm/yyyy

8.5.2 Storage

Keep the ampoules in an upright position.
Do not freeze the ampoules.
Do not store the ampoules above 30°C.
Store the ampoules in the original packaging.
Store the ampoules in the foil envelope to protect them from light.

8.6 Inhalation Device Packaging

The device package consists of the PARI SINUS Compressor (230V/50Hz), the PARI LC SPRINT SINUS nebuliser (incl. nose plug and nasal joining piece), the SINUS Instruction for Use and the SINUS Flyer “Use & Hygiene”.

8.7 Duration of Patient Participation

Each patient will receive once or twice daily IMP treatment for 8 weeks (2 months). During study participation, 7 visits at the clinical trial centre are scheduled (see Study Flow Chart).

8.8 Stopping Rules and Discontinuation Criteria

8.8.1 Study Level

The study will be considered complete when 20 randomised patients have completed the study. The Sponsor may terminate the study before regular completion if the safety of any patient is a concern or a significant delay in patient recruitment occurs or for administrative reasons.

8.8.2 Centre Level

The Sponsor may close a centre, if 12 weeks after centre initiation no patient has been enrolled or if the enrolment rate is significantly reduced. The centre will be closed when the study is considered complete (see Section 8.8.1 for details).

8.8.3 Patient Level

A patient will be considered to have completed the study after having passed the control visit at Week 48 after starting treatment with IMP.

Patients will be removed from the study for the following reasons:

- Subjects may discontinue participation in the study at any time.
- The Principal Investigator may withdraw a subject at any time if it is in the best interest of the patient based upon clinical assessments or if the subject fails to comply with the protocol.

If the study participant fails to take experimental medication or the patient fails to return for clinical follow-up the subject will be reached by telephone or a letter will be sent requesting a mandatory clinic visit and the reason for non-compliance shall be documented.

8.9 Investigational Medicinal Product Supply and Accountability

The Investigator is responsible for ensuring that deliveries of IMP ampoules and boxes, PARI SINUS devices and other study materials from the Sponsor are correctly received and recorded, that these are handled and stored safely and properly, and that they are used in accordance with this protocol.

Unused IMP ampoules (opened, unopened, or empty), boxes and PARI SINUS devices must be returned to the Sponsor, if appropriate, after the study and overall drug accountability has been completed. A list of IMP, PARI SINUS devices and other materials received, used, returned, or destroyed must be prepared and signed by the Principal Investigator; any discrepancies must be accounted for.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Patient Inclusion Criteria

Patients are included in the study if all of the following criteria are met:

1. Patient with confirmed diagnosis of chronic rhinosinusitis (CRS), i.e. inflammation of nasal mucosa and paranasal sinus. Diagnosis is based on history of symptoms (nasal obstruction, running nose, postnasal drip, facial pain and hyposmia with a duration of > 3 months (according to EPOS3) and on MRT-imaging (Lund-Mackey Score [Score: 0-24])
2. Patient without alternative other than sinus surgery
3. Patient's written informed consent obtained prior to any screening or study-specific procedure
4. Male or female, ≥ 18 years of age
5. Patient is able to undergo nasal therapy without restrictions
6. Capable to correctly use the PARI SINUS device (closing of the soft palate) in accordance with the package insert
7. Capable of understanding the purpose and risk of the clinical trial
8. 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.
9. Patient is able to participate in the study according to Investigator's opinion

9.2 Patient Exclusion Criteria

Patients are excluded from participating in this study if one or more of the following criteria are met:

1. Patients with cystic fibrosis
2. Patients with polyposis nasi grade I-IV (according to Rasp et al. 2000)
3. Patients with prior FESS (Functional Endosopic Sinus Surgery)
4. Pregnant or breastfeeding women
5. Any active invasive bacterial, viral or fungal infection within one week prior to first investigational medicinal product (IMP) administration
6. No clinically relevant abnormal parameters of vital signs, blood biochemistry or renal/hepatic function
7. Unlikely to comply with visits, inhalation procedures or other measurements scheduled in the protocol
8. Receipt of an investigational drug as part of a clinical trial within 4 weeks prior to first administration of IMP

9. Any co-existing medical condition that in the Investigator's judgement will substantially increase the risk associated with the patient's participation in the clinical trial
10. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary procedures
11. Drug or alcohol abuse
12. End-stage malignancies
13. Known hypersensitivity to Budesonide
14. Patients with oral steroid therapy within the last 3 months
15. Patients needing > 1 mg/day Budesonide (or steroidal equivalent) for therapy of asthma
16. Patients on therapy with leukotriene-receptor antagonists, decongestants, antihistamines or antibiotics
17. Patients with frequent epistaxis (> 1 episode per week)

9.3 Withdrawal Criteria and Procedures, Interruption or Discontinuation of Study

The patient is free to withdraw from the study for any reason and at any time without giving a reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a patient's involvement in the study at any time if the patient's clinical condition warrants it.

In order to support the Investigator in his/her decision to withdraw a patient, it is recommended to use the standard common toxicity criteria (CTC), version 3.0 as the basis for evaluation. If a grade 3 or 4 toxicity occurs to the patient, the Investigator should consider withdrawing the patient from the IMP therapy.

It is also possible that the Sponsor or the Competent Authorities request termination of the study if there are concerns about conduct or safety.

Patients who withdraw voluntarily, or who are discontinued from the study prior to Visit 6 (end of study visit, Week 48) should have all final study visit procedures performed if possible (see Section 13.14).

All patients withdrawn from the study will be followed-up for AEs and SAEs for further 2 weeks or 4 weeks, respectively. Any patient with ongoing SAE(s) will be followed-up until recovery or stabilisation of the SAE(s).

Reasons for withdrawal are:

- Revoke of informed consent by the patient or patient's legal representative
- Investigational treatment or the study procedures present an unacceptable medical risk to the patient
- Patient fails to comply with protocol procedures

The reasons for withdrawal should be recorded in the CRF.

In the event of patient withdrawal the Investigator must complete the provided screening and enrolment log stating the reason and date of withdrawal.

Patients who have consented to participate but who are withdrawn for any reason before randomisation will be replaced until the scheduled number of randomised patients has been achieved. Randomised patients who do not complete the study as scheduled for any reason and at any time will not be replaced.

9.4 Completion of Study and Loss to Follow-up

Patients will be considered to have completed the study if they were followed-up through Study Visit 6 (Study Week 48). It should be specified on the CRF whether or not the patient completed the study follow-up procedures through Study Week 48.

A patient will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at Visit 6 (Study Week 48). The Investigator should document attempts to re-establish contact with any missing patient throughout the study period. If contact with a missing patient is established, follow-up should resume according to the protocol.

10. TREATMENT OF SUBJECTS

10.1 Buparid/PARI SINUS

Following screening and consenting, all participants regardless of treatment allocation will receive Budes® Nasal Spray 50 µg (2 pumps/nostril BID) in a 1-week Wash-in Phase before starting the IMP-treatment to prevent a bias of study results due to former individualised therapies. The study will enrol subjects who typically have received several different therapies with steroidal nasal sprays or drops. These therapies may be based on different steroidal substances. The Wash-in Phase intends to homogenize treatment to budesonide before administering the investigational treatments.

After passing the Wash-in Phase patients randomised to receive Buparid/PARI Sinus will be treated as follows:

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

The patients will be observed for a total of 12 months.

10.2 Budes® Nasal Spray

Following screening and consenting, all participants regardless of treatment allocation will receive Budes® Nasal Spray 50 µg (2 pumps/nostril BID) in a 1-week Wash-in Phase before starting the IMP-treatment to prevent a bias of study results due to former individualised therapies.

After passing the Wash-in Phase patients randomised to receive Budes® Nasal Spray will be treated as follows:

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.

The patients will be observed for a total of 12 months.

10.3 Concurrent Treatment or Medication

Apart from the randomly allocated study medication, no other specific therapies for the treatment of CRS are prescribed during the study period (**especially use of saline nasal irrigation solutions during IMP treatment phase**).

However, any other treatment required during study period and prior to first IMP administration will be recorded in the CRF until last study visit (Visit 6).

All other concurrent treatment or medication, including all procedural medication given before, during, and after the examination, will be recorded in the CRF. The tradename, and dosage should be documented. All treatment and medication will be encoded according to MedDRA in its current version.

During the whole study, the use of systemic corticosteroids is prohibited.

A patient may receive medications to treat AEs as deemed necessary by the Investigator or the patient's physician.

10.4 Procedures for Monitoring Patient Compliance

At each visit, the patient's compliance to the inhalation procedure (Section 8.4.3) will be monitored by the clinical trial centre personnel by supervising one inhalation cycle. A patient will be regarded as compliant if no more than 20% of inhalations of IMP treatment according to protocol are missed. The patients have to hand out used Buparid ampoules and Budes® Nasal Sprays at each study visit in order to allow for drug accountability.

Any time the patient has not the ability to inhale, due to e.g. AEs will not be considered in the compliance calculation. The reason for non-compliance shall be documented accordingly in the CRF.

11. ASSESSMENT OF EFFICACY

11.1 Efficacy Parameters

Parameters to determine efficacy of the corticosteroidal treatment include:

- Health-related quality of life
- Nasal obstruction
- Inflammation of nasal mucosa and paranasal sinus
- Clinical parameters
- Symptoms of rhinosinusitis
- Loss of taste/Loss of smell
- Avoidance or postponing of sinus surgery
- Customer satisfaction regarding the PARI SINUS device, if applicable

11.2 Methods and Timing of Efficacy Assessments and Procedures

11.2.1 Health-related quality of life (at Weeks -1, 0, 4, 8, 12, 24, and 48)

Assessments will be done on all study visits (Visit 1 through Visit 6) using the Sino-Nasal outcome Test 22 (SNOT 22).

11.2.2 Nasal obstruction (at Weeks -1, 0, 4 and 8)

Nasal obstruction will be assessed using the method of rhinonanometry by measuring the positive nasal inspiratory flow (PNIF). Assessment will be done prior to Wash-in Phase (at Visit 1), prior to commencement of study medication (at Visit 2), during treatment (at Visit 3) and after end of treatment (at Visit 4). At each assessment the subject has to inhale maximally through the nose three times and the highest value will be recorded.

11.2.3 Inflammation of the nasal mucosa and paranasal sinus (at Weeks 0 and 8)

Inflammation of the nasal mucosa and paranasal sinus will be assessed be determination of the thickness of the mucosa using Magnetic Resonance Imaging (MRI) at Visits 2 and 4. The results will be interpreted using the Lund-Mackay-Score:

Table 11.2-1: Lund-Mackay staging system

Paranasal sinuses	Right	Left
Maxillary (0, 1, 2)		
Anterior Ethmoid (0, 1, 2)		
Posterior Ethmoid (0, 1, 2)		
Sphenoid (0, 1, 2)		
Frontal (0, 1, 2)		
Ostiomeatal complex (0*, 2*)		
Total points to each side		

0 = no abnormalities; 1 = partial opacification; 2 = total opacification; 0* = not occluded; 2* = occluded

11.2.4 Clinical Parameters (Endoscopic Appearance Score) (at Weeks -1, 8 and 48)

The Appearance Score will be assessed endoscopically at Visit 0, 3 and 6 and interpreted according to Lund et al. 1995.

Table 11.2-2: Endoscopic Appearance Score

Endoscopic Appearance	Score
Polyposis left	0 = No visible polyps 1 = Polyps located interior of the middle nasal meatus 2 = Polyps located exterior of the middle nasal meatus
Polyposis right	0 = No visible polyps 1 = Polyps located interior of the middle nasal meatus 2 = Polyps located exterior of the middle nasal meatus
Oedema left	0 = No oedema 1 = Mild oedema 2 = Severe oedema
Oedema right	0 = No oedema 1 = Mild oedema 2 = Severe oedema
Nasal discharge left	0 = No discharge 1 = Clear, serous discharge 2 = Mucopurulent discharge
Nasal discharge right	0 = No discharge 1 = Clear, serous discharge 2 = Mucopurulent discharge
	Total Score: 0 - 12

11.2.5 Symptoms of rhinosinusitis (at Weeks -1, 0, 4, 8, 12, 24 and 48)

Symptoms of rhinosinusitis will be documented at Visits 0, 1, 2, 3, 4, 5 and 6. Parameters to be assessed include:

- Nasal obstruction (see 11.2.2)
- Rhinorrhoea
- Loss of smell/taste (see 11.2.5)
- Facial pressure pain (by means of a Visual Analogue Scale (VAS)

  Visual Analogue Scale:

  Each subject will be asked to indicate the answer to the question “How troublesome are your symptoms of rhinosinusitis?” on a 10 cm visual analogue scale (Not troublesome → Most troublesome imaginable).

11.2.6 Loss of taste/Loss of smell (at Weeks -1, 0, 8 and 48)

Loss of taste will be assessed using taste strips at Visits 0, 1, 3 and 6. Loss of smell will be assessed using sniffing sticks at Visits 0, 1, 3 and 6.

11.2.7 Avoidance or postponing of sinus surgery (at Weeks -1, 8, 12, 24 and 48)

- Time to sinus surgery (as calculated from randomization onwards)

12. ASSESSMENT OF SAFETY

12.1 Safety Parameters

The following safety parameters will be assessed:

- Treatment-emergent adverse events (AEs)

12.2 Methods and Timing of Safety Assessments and Procedures

12.2.1 Pregnancy Test

Pregnancy tests will be obtained in women of childbearing potential only. A urine pregnancy test will be obtained prior to first IMP administration.

12.2.2 Adverse Events

12.2.2.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product 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), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidelines for Good Clinical Practice, May 1996).

This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition. An adverse event is considered serious if it meets any of the serious criteria listed below. To ensure no confusion or misunderstanding of the difference between the terms “serious” and “severe”, which are not synonymous, the following clarification is provided:

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

The official definition also extends to AEs occurring under placebo or in a reference group receiving drug or non-drug therapy.

A baseline recording of any symptoms of illness will be performed before administration of the IMP. Only symptoms that increase in severity after study drug administration or new symptoms of illness will be recorded as AE in the CRF.

Each patient will be closely observed and questioned for AEs during the study procedures and throughout the study period with non-leading questions (e.g. how do you feel?). The patients will be instructed to report to the study staff immediately any symptoms and/or signs which occur between the scheduled observation times.

All AEs reported by the patient or observed by the Investigator or hospital personnel will be

reported in the CRF. The following information regarding each adverse event will be obtained: date and time of onset and resolution (duration), serious or non-serious (as defined below), severity, treatment required, outcome, relationship to study drug, and if the AE caused withdrawal from the study.

In addition to the Investigator's own description of the AE, each AE event will be coded according to the MedDRA code list in its current version. The verbatim term will be recorded in the CRF.

Adverse Reaction (AR)

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. An unexpected ADR is any adverse reaction not identified in nature or intensity in the current Summary of Product Characteristics (SmPC).

Serious Adverse Events (SAEs)

A SAE is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (immediate risk of death at the time of the event)
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
- Other: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

12.2.2.2 Relationship to Study Drug

An AE will be considered as AR, if a causal relationship to the administration of IMP cannot be excluded, e.g. if the relationship is possible, probable or very likely according to the following definitions:

- **Not related**: An AE that is not related to the use of the investigational product
- **Doubtful**: An AE for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely
- **Possible**: An AE that might be due to the use of the investigational product. An alternative explanation e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded

- **Probable**: An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s)
- **Very likely**: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge)

12.2.2.3 Maximum Intensity

The severity of all adverse events will be evaluated as mild, moderate or severe using the following definitions:

- **Mild**: The event is easily tolerated
- **Moderate**: The event interferes with normal activity
- **Severe***: The event is incapacitating (causes inability to perform usual activity or work)

* There is a distinction between a severe adverse event and a serious adverse event; a severe reaction is not a serious adverse event unless it meets one of the criteria for serious events (see Section 12.3.1).

12.2.2.4 Serious Adverse Event (SAE) Reporting

Any serious adverse events occurring

- between the first clinical trial procedure and within 4 weeks after the completion of the EOS visit, whether or not considered related to the study drugs;

or

- at any time after completion of the last follow-up and coming to the attention of the Investigator, if it is judged as related to the patient's participation in the study

must be reported to the Sponsor's SAE Safety Officer within 24 h, as follows:

- Report all SAEs within 24 h of discovery of the event to the Safety Officer (indicated below) by telephone or fax
- Complete a supplemental SAE Form and send it to the Sponsor's Safety Officer within 24 h after the discovery of the event
- Follow-up the SAE until the outcome is determined, providing periodic updates to the Safety Officer as requested
- Record the SAE in the patient's CRF on the AE page
- Provide any additional information if requested

The Safety Officer must be notified by telephone when a document has been sent by fax. If limited information on the event is initially available, follow-up reports will be required. Each SAE should be reported to the EC and the local health authorities by the Principal Investigator, according to local regulations.

SAE Safety Officer **Dr. Rafaël Smetss** **SGS Life Science Services** **Mechelen Noord zone L** **Intercity Businesspark** **Generaal De Wittelaan 19A bus 5** **2800 Mechelen** **Belgium**	**Fax: +32 (0)15 29 93 38** **Phone: +32 (0)15 29 93 94** **E-mail: be.life.SAEprocessing@sgs.com**

12.2.2.5 Other Events to be Treated as Serious Adverse Event (SAE)

Exposure to drug during pregnancy/lactation:
In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of the study, the patient must be withdrawn from all IMP treatment immediately. The Investigator should report pregnancy cases occurring during the clinical trial to SGS Life Science Services Medical Affairs immediately using the SAE form. PARI Pharma GmbH must be notified without delay. Pregnancy cases will be followed-up during the entire course of the pregnancy and postpartum period using SGS Life Science Services Drug Exposure during Pregnancy – Pregnancy Form A and End of Pregnancy – Pregnancy Form B. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. The SAE reporting procedure should be followed, even though pregnancy is not considered a SAE. No "serious criterion" should be checked. The SAE report form is solely used to ensure expedited reporting.

12.2.2.6 Investigational medicinal product (IMP) overdosing

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. For the purposes of this study, any dose of aerosolised IMP administered to a patient that exceeds the dose foreseen in the protocol by more than 50% over 4 weeks should be reported as an overdose. It must be reported as an SAE, irrespective of outcome and even if toxic effects were not observed.

12.2.2.7 Events Not Regarded as Adverse Events/Serious Adverse Events

The following events will be not regarded as AEs/SAEs:

- Pre-scheduled (before any trial-related activity) hospitalisations/surgeries/interventions
- Trial endpoint-related worsening; these will be assessed as treatment success or failure during trial endpoint analysis

The Sponsor's responsibilities in regards to reporting SAEs and Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) are in accordance with European Directive 2001/20/EC.

12.2.3 Monitoring of Adverse Events

Any patient experiencing AEs, whether ascribed to the IMP or not, will be followed closely until the outcome is determined in addition to the EOS visit to assess adverse events. All AEs must be documented in the patient's medical record. The occurrence of AEs and SAEs will be monitored until 2 and 4 weeks after the EOS visit, respectively. Any patient with ongoing SAEs will be followed up until recovery or stabilisation of the SAE.

13. VISIT SCHEDULE

All investigations and activities are listed in the flowchart and trial overview (Section 8.2) of the clinical trial protocol. Further details on the methodology of these investigations and activities are described in detail in Sections 8.1 through 8.2. The Investigator should adhere to the visit and procedure schedule as closely as possible.

All patients assigned a randomisation number and who receive any IMP treatment will be followed according to the protocol regardless of the number of IMP received, unless consent for follow-up is withdrawn. The Sponsor must be notified of all deviations from the protocol visit schedule or evaluations and these visits/evaluations, if applicable, must be rescheduled or performed at the closest possible time to the original schedule.

Patients will be instructed to call study personnel to report any abnormalities, including any hospitalisations or doctor visit, during the interval between study visits and to come to the study site if medical evaluation is needed and urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records of the visit should be obtained by the Investigator.

If a patient prematurely discontinues from the study for any reason, e.g. the patient withdraws consent for further participation in the study, the Sponsor will request that the evaluation listed under "Final Visit (EOS) for Patients who Prematurely Discontinue from the Study" (see Section 13.14) be completed prior to discontinuation.

13.1 Study Visits

A schedule of screening and study visit procedures is presented in section 8.2.1 (trial overview), followed by a detailed description of each visit.

13.2 Screening and Baseline Visit 0 (Week -1)

The Investigator must assess the following procedures:

Written informed consent must be obtained from each patient or patient’s representative according to local law prior to entering the clinical trial. The patient MUST give his/her original signature with date and time on the patient information/consent form.

It should be marked in the hospital files that the patient is participating in a clinical study, including patient's ID, demographic data, date of inclusion and number of study.

After the Investigator has obtained written informed consent from the patient, the following assessments will be made:

- Evaluate eligibility for the study per the inclusion/exclusion criteria
- Pregnancy tests will be obtained in women of childbearing potential only. A urine pregnancy test will be obtained at screening.
- Demographics: year of birth, gender, race, date of body measurements, height, weight, nicotine and alcohol consumption
- Medical history: underlying condition, antiviral/antifungal/antibacterial therapy

- IMP administration (Budes® Nasal Spray for Wash-in)
- Health-related quality of life
- Nasal obstruction
- Endoscopic Appearance Score
- Symptoms of rhinosinusitis
- Loss of taste/Loss of smell
- Requirement of surgery
- Other concomitant treatment: name of drug, dosage, duration
- AEs (baseline signs and symptoms)

13.3 Visits 1 (Week 0)

The Investigator must assess the following:

- IMP administration
- Health-related quality of life
- Nasal obstruction
- Inflammation of nasal mucosa and paranasal sinus
- Symptoms of rhinosinusitis
- Loss of taste/Loss of smell
- Other concomitant treatment: name of drug, dosage, duration
- AEs

13.4 Visits 2 (Week 4)

The Investigator must assess the following:

- IMP administration
- Inhalation compliance
- Health-related quality of life
- Nasal obstruction
- Symptoms of rhinosinusitis
- Other concomitant treatment: name of drug, dosage, duration
- AEs

13.5 Visit 3 (Week 8)

The Investigator must assess the following:

- Inhalation compliance

- Health-related quality of life
- Nasal obstruction
- Inflammation of nasal mucosa and paranasal sinus
- Endoscopic Appearance Score
- Symptoms of rhinosinusitis
- Loss of taste/Loss of smell
- Requirement of surgery
- Other concomitant treatment: name of drug, dosage, duration
- AEs

13.6 Visits 4 (Week 12)

The Investigator must assess the following:

- Health-related quality of life
- Symptoms of rhinosinusitis
- Requirement of surgery
- Customer satisfaction regarding the PARI SINUS device, if applicable
- Other concomitant treatment: name of drug, dosage, duration
- AEs

13.7 Visit 5 (Week 24)

The Investigator must assess the following:

- Health-related quality of life
- Symptoms of rhinosinusitis
- Requirement of surgery
- Customer satisfaction regarding the PARI SINUS device, if applicable and not done at Visit 4
- Other concomitant treatment: name of drug, dosage, duration
- AEs

13.8 Visit 6 (Week 48)

The Investigator must assess the following:

- Health-related quality of life
- Endoscopic Appearance Score
- Symptoms of rhinosinusitis

- Loss of taste/Loss of smell
- Requirement of surgery
- Other concomitant treatment: name of drug, dosage, duration
- AEs

14. STATISTICS

14.1 Statistical Concept

This is the first study using the drug/device combination Buparid/PARI SINUS for treatment of CRS. 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 will not be powered for a confirmatory proof of a clinically meaningful effect.

Technical details of data analysis and presentation of the results will be provided in a Statistical Analysis Plan (SAP) that will be finalized before the execution of any analyses that will provide efficacy or tolerability results broken down by treatment.

14.2 Sample Size Considerations

Due to the current lack of availability of data required for the design of a confirmatory clinical trial, this pilot trial is intended to create sufficient data for a formal calculation of sample size and statistical hypotheses in a clinical investigation at a later phase of drug development (phase III).

In this pilot study the determination of the sample size is primarily based on feasibility rather than on statistical reasons. It is intended to randomize a total of 20 patients. Ten patients will be randomized into the Buparid/PARI SINUS arm and 10 into the Budes® Nasal Spray arm. When the sample size in each group is 10 patients, a two-sided 95% confidence interval for the difference between the treatment groups' mean values will extend ±0.88 standard deviation units from the point estimate.

14.3 Missing Data

The investigators should take every effort to assure complete data. Of note, patients withdrawn from treatment prematurely for any reason should be attempted to be followed up until the scheduled end of the observational period unless they withdraw their informed consent or further participation in the follow-up presents an intolerable medical risk.

The 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. Other missing data imputation techniques may be defined in the context of explorative analyses as needed.

14.4 Analyses of Patient 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 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 Statistical Analysis Plan (SAP) as well as in the integrated clinical study report.

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 analysed in the SAS.

14.5 Statistical and Analytical Methods

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 group 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.

14.6 Baseline Comparability

Demographic data for age, height and weight will be summarized using descriptive statistics as noted above. Subject randomization, duration of treatment, subject disposition, drug

compliance and protocol violations and reason will be described.

Prior medications within 2 weeks before Wash-in as well as any concomitant medication, relevant previous and any ongoing concurrent diseases will be coded according to medical standard dictionaries (WHO-DD and MedDRA) and will be summarized by treatment group.

14.7 Analysis of Efficacy

Treatment efficacy will be analysed by performing treatment group comparisons for the efficacy outcome measures identified in Section 11. For outcome measures assessed at and after baseline, absolute and relative differences to the baseline value will be calculated.

Since the study's sample size has not been determined based on power considerations (see Section 14.2), and the concept of the trial is exploratory in nature (Section 14.1), p-value-based comparisons are not of primary importance. The estimation of the treatment effects to be expected in a confirmatory trial for the different outcome measures will be based on determining 95% confidence intervals for the differences between the treatment groups' mean values, medians, or rates.

14.8 Analysis of Safety

Safety data will be collected for all subjects from study inclusion until Week 48 (end of follow-up). The analysis of safety will be based on adverse events (as defined in Section 12.2.2) that are reported by the patients spontaneously or upon elicitation, which will be performed during all visits starting at baseline.

Adverse events will be MedDRA coded and will be summarized by severity and relationship to the investigational treatment administered.

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.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilms or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case report forms, all copies of test results, and study-related regulatory documents [e.g., Informed Consents, Ethics Committee (EC)/Institutional Review Board (IBR) approvals/correspondence, etc.] must be available at all times for regulatory agency inspection and review by the Sponsor or its designee. During the periodic site monitoring visits, the source documents will be verified against data entered onto the CRF in order to assure that all data is accurately and completely reflected on the patient's CRF.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Amendments and Protocol Violations

No changes from the final approved (signed) protocol will be initiated without the EC's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the patients or when the change involves only logistics or administration. The Principal Investigator(s) at the clinical trial site and the Sponsor sign the protocol amendment.

The Principal Investigator is responsible for submitting any and all protocol deviations, violations or non-compliance issues that occur during the course of the study.

- **Major protocol deviations and violations -** will be documented and submitted to the ECs no later than 7 days of discovering them. If the deviation has potential to affect patient safety it must be reported immediately.
- **Minor protocol deviations and non-compliance** – These deviations should be documented in the study file and will be reported to the EC according to local requirements.

16.2 Information to Study Personnel

The Investigator(s) is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the practical performance of the study and during the course of the study (e.g., when new staff become involved).

The monitor(s) is responsible for explaining the protocol to all staff assisting the Investigator and for ensuring their compliance with the protocol. Additional information available during the study should be given as agreed upon, either by the Investigator(s) or the monitor (s), and always when new staff becomes involved in the study.

16.3 Clinical Trial Monitoring

A monitor from PARI Pharma GmbH or designee will contact and visit the Investigator intermittently during the trial. Each clinical site will be monitored within 4 weeks of randomisation of its first patient. The average monitoring frequency is expected to be one visit quarterly but this may be adjusted for the actual recruitment rate or for communication purposes, depending on the enrolment rate and outstanding issues or queries at the site. The monitor(s) or representative is responsible for ensuring that the study is conducted according to SOPs to ensure compliance with ICH-GCP.

The monitor(s) is the primary link between the Sponsor and the Investigator. The main responsibilities of the monitor(s) are to visit the Investigator before, during, and after the study to ensure adherence to the protocol, and to assure that all data are correctly and completely recorded and reported and that informed consent is obtained and recorded for all patients before their participation in the study.

The monitor(s) will contact and visit the Investigator at regular intervals throughout the study. The monitor(s) will be allowed to check and verify the various records (CRFs and other

pertinent data records) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of the study progress other Sponsor personnel may, upon request, accompany the monitor(s) on visits to the study centre. The Investigator and assisting staff must agree to co-operate with the monitor(s) to resolve any problems, errors, or possible misunderstandings concerning the data detected in the course of these monitoring visits.

During the monitoring visit, the following items must be accessible for review:

- Source documents, including informed consent forms, for all screened patients Investigator Site File (100% source data verification will be conducted)
- CRFs for all patients
- Drug accountability logs
- Drug supply and clinical supply cabinets
- Storage of lab samples
- All study staff will also need to make themselves available for review of monitoring issues

16.4 Audit and Inspection

According to ICH Guidelines on GCP, the Sponsor or their legal representatives may audit the investigational site to compare raw data, source data, and associated records with the interim or final report of the study to assure that data have been accurately reported. The Sponsor's quality assurance unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The Investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

In addition, regulatory bodies and their discretion may conduct inspection.

17. ETHICAL AND REGULATORY ASPECTS

The protocol will be reviewed and approved by the EC of each participation centre prior to study initiation.

Serious adverse events regardless of causality will be reported to the Sponsor within 24 h and to the EC, and the Investigator will keep the EC informed as to the progress of the study. The Investigator will explain the nature of the study and will inform the patient that participation is voluntary and that the patient can withdraw at any time. Written informed consent will be obtained for each patient prior to entry into the study. A copy of the signed consent form will be given to the patient and the original will be maintained with the patient's record.

17.1 Responsibilities of the Investigator

The Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki as well as with the ICH guideline E6 GCP: Consolidated Guideline and applicable regulatory requirements. These documents state that the informed consent of patients is an essential precondition for participation in the clinical study.

17.2 Patient Information

An unconditional prerequisite for a patient participating in the study is his/her written informed consent. Adequate information must therefore be given to the patient by the Investigator before informed consent is obtained. A person designated by the Investigator may give the information, if permitted by local regulations. A patient information sheet (informed consent document) in the local language and prepared in accordance with the ICH E6 will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to this written information, the Investigator or his designee will inform the patient verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons.

The patient information sheet will be revised whenever important new information becomes available that may be relevant to the consent of patients.

17.3 Patient Informed Consent

This study will be conducted in full accordance with the current revision of the Declaration of Helsinki and the *GCP: Consolidated Guideline* approved by the ICH.

The written informed consent of the patient to participate in the clinical study has to be given before any study-related activities are carried out on the patient. It must be signed and personally dated by the patient and by the Investigator/person designated by the Investigator to conduct the informed consent discussion.

Provision of consent will be confirmed in the CRF by the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation.

This study will be conducted in compliance with ICH Guidelines for informed consent. Information should be given in both oral and written form, and patients or their legal representative must be given ample opportunity to inquire about details of the study. Writing consent documents will embody the elements of informed consent as describe in the Declaration of Helsinki and will also comply with local regulations.

Patients must be informed about the aims, expected benefits, and possible risks (including the statements that the particular treatment or procedure may involve risks to the patients that are currently unforeseeable). They must also be informed of alternative procedures. Patients must receive explanation as to whether any compensation or medical treatments are available if injury occurs, and if so, what they consist of, or where further information may be obtained. They must be informed whom to contact for answers to any question relating to the research project. Patients must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled. The extent of confidentiality of the patient's record must be defined, and patients must be informed that applicable data protection legislation will be complied with. Patients must be informed that monitors(s), auditors(s), EC members, and regulatory authorities will be granted direct access to the patient's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a writing informed consent form, the patient's legally acceptable representative is authorised such access.

The patient's representative willingness to participate in the study will be documented in writing in a consent form, which will be signed by the patient's legal representative and the person performing the informed consent procedure with the date and time of that signature indicated. The Investigator(s) will keep the original consent forms and copies will be given to the patients.

Written and/or oral information about the study in a language understandable by the patient's legal representative will be given to all legal representatives. The information provided must include an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force.

17.4 Subject Insurance

The Sponsor confirms that an insurance covering the costs of treatment of trial subjects in the event of trial-related injuries according to applicable regulatory requirements in the participating countries has been arranged by the Sponsor.

No other compensation (such as lost wages or payment for emotional distress) will be provided by the Sponsor.

17.5 Ethics

This trial will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association.

The planning and conduct of this trial follows the respective national laws of the participating countries, the principles and guidelines for good clinical practice laid down in Directives

2001/20/EC and 2005/28/EC of the European Parliament and the Consensus paper of the International Conference on Harmonisation on good clinical practice (ICH-GCP) and the PARI Pharma GmbH SOPs that are based on the ICH-GCP guidelines.

17.6 Notification to Competent Authorities (CA) and Ethics Committees (EC)

17.6.1 Commencement of the Trial

Before commencing the trial in any trial centre, the Sponsor will submit a valid request for authorisation to the CA in the participating countries including this protocol and a summary of essential pharmacological-toxicological and clinical data.

In parallel, the Sponsor will submit a valid application to the competent ECs to give its opinion on the study protocol and the written subject information/informed consent.

The constitution of the competent EC must meet the requirements of the participating country. A list of the EC members, with names and qualifications, will be requested. If such a list is unavailable, the Investigator must provide the name and address of the EC along with a statement from the EC that it is organised according to GCP and the applicable laws and regulations. The EC must also perform all duties outlined by the requirements of the participating country.

The study will not start until the competent EC has issued a favourable opinion (positive vote) and if the CA in the country concerned has not informed the Sponsor of any grounds for non-acceptance.

17.6.2 Ending of the Trial

Within 90 days of the end of the trial, the Sponsor will notify the CAs concerned and the ECs that the clinical trial has ended. If the trial has to be terminated early, the notification period will be reduced to 15 days and the reasons will be explained.

17.6.3 Notification to Local Authorities

According to local law, the conduct of this trial will be notified to the respective local authorities as well as the name and address of each Investigator.

17.6.4 Protocol Amendment

Should any change be required to the signed, final protocol, a protocol amendment will be required. The amendment must be signed by the project managers of the Sponsor and, if necessary, by the statistician.

Substantial amendment

If this amendment is substantial and is likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if it is otherwise significant, the Sponsor will notify the CAs of the Member State or the Member States concerned of the reasons for and content of this amendment and will inform the EC or ECs concerned.

Should the opinion of the EC be favourable and the Competent Authorities of the Member States have raised no grounds for non-acceptance of the above-mentioned substantial

amendment, the Sponsor will proceed to conduct the clinical trial following the amended protocol.

If the opinion of the EC is unfavourable, the Sponsor will not implement this substantial amendment to the protocol. The Sponsor will either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment.

Non-substantial amendments

Protocol amendments only for logistical or administrative changes may be implemented immediately; the EC will be informed by the Sponsor accordingly.

Urgent safety measures

If any new event relating to the conduct of the trial or the development of the investigational medicinal product occurs that is likely to affect the safety of the subject, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the subjects against any immediate hazard. The Sponsor will inform the CAs of this new event and the measures taken immediately and will ensure that the EC is notified at the same time.

17.7 Confidentiality Regarding Study Patients

All local legal requirements regarding data protection will be adhered to.

All drug-related information obtained by the Investigator and supplied by the Sponsor is to be treated as confidential by the Investigator and all other personnel involved in the trial. Third persons who are not participating in or working on this clinical trial are not authorised to receive any trial data or material.

The anonymity of participating subjects must be maintained and study findings will be treated confidentially. Throughout documentation and evaluation, the subjects will be identified on CRFs and other documents by their birth date, and their identification number (pseudonymous data recording). The subjects will be informed that all study findings will be stored on a computer and handled in the strictest confidence.

18. DATA HANDLING AND RECORD KEEPING

18.1 Source Documents and Data's Recorded on the Case Report Form

Patient participation (e.g. number of study, patient's ID, date of inclusion, date of completion and adverse events) must be recorded in the patient's medical record according to Good Clinical Practice.

Any data recorded directly on the Case Report Form (CRF), for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data (e.g., body measurements or the drug administration procedure).

The Investigator shall permit Sponsor, authorised agents of the Sponsor, and regulatory agency employees to enter and inspect any site where drug or records pertaining to the drug are held, and inspect and copy all records relating to an investigation, including patient records.

Completed CRFs must be made available by the Investigator for review by the Sponsor, agent of the Sponsor, clinical monitor and regulatory agency. To ensure the accuracy of data submitted, it is mandatory that representatives of the Sponsor and regulatory agencies have direct access to source documents (patient medical records, charts, laboratory reports etc.).

Patient confidentiality will be protected at all time.

18.2 Case Report Forms

The CRF and the protocol are both confidential. The CRF will remain the property of the Sponsor at all time.

- The Sponsor will supply the CRFs. The original is to be returned to the Sponsor and a copy left with the Investigator.
- All CRFs are to be completed by the examining personnel and reviewed and signed by the Investigator(s).
- All CRFs are to be completed in a neat, legible manner to ensure accurate interpretation of data. The CRF must be completed in black pen to ensure clarity of any reproduced copy of all CRFs.
- Any changes or corrections made on the CRFs must be dated and initialled by the person making the changes. In such cases, the best procedure is to cross out the original entry using a single line. DO NOT ERASE, OVERWRITE, OR USE LIQUID PAPER ON ORIGINAL CRF ENTRIES.
- It is each Investigator's responsibility to ensure that all DISCONTINUED orders or changes in the study or other medications entered on the patient's CRF correspond to entries in the patient medical records.
- CRFs for any patient leaving the study should be completed at the time medication is terminated for whatever reason.
- CRFs must accurately reflect data contained in the patient's medical records (e.g. source documents).

18.3 Case Report Form (CRF) Handling

The main objective is to obtain those data required by the study protocol in a complete, accurate, legible, and timely fashion. The data in the CRF should be consistent with the relevant source documents.

The data recorded in the course of this study must be documented in the CRFs and must be forwarded to the Sponsor or designee. They shall then be processed, evaluated, and stored in anonymous form in accordance with the data-protection regulations.

The Investigator must ensure that the CRFs forwarded to the Sponsor or designee and any other associated documents contain no mention of any patient names.

The CRFs must be filled in completely and legibly (with either black or blue ballpoint pen, acceptable for use on official documents). Any amendments and corrections necessary must be undertaken and countersigned by the Investigator or designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids (e.g., Tipp-Ex®). The patient's medical source documents must support any changes made.

In the case of missing data/remarks, the entry spaces provided for in the CRF should be cancelled out so as to avoid unnecessary follow-up inquiries. The CRFs are regulatory documents and must be suitable for submission to authorities.

18.4 Source Data and Patient Files

The Investigator has to keep a written or electronic patient file for every patient participating in the clinical study. In this patient file, the available demographic and medical information of a patient has to be documented, in particular the following: name, date of birth, sex, height, weight, patient history, concomitant diseases and concomitant medication (including changes during the study), statement of entry into the study, study identification, randomisation number, the date of informed consent, all study visit dates, pre-defined performed examinations and clinical findings, observed AEs (if applicable) and reason for withdrawal from study treatment or from the study (if applicable). It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file. It must be possible to identify each patient by using this patient file.

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. This may include laboratory value listings, ECG recordings, X-rays, CT scans, etc. (if applicable). All these documents have to bear at least the patient identification and the printing date printed by the recording device to indicate to which patient and to which study procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the Investigator.

Printouts of computerised patient files must be signed and dated by the Investigator, countersigned by the monitor, and kept with the Investigator's copy of the CRF as a source document.

18.5 Investigator File and Archiving

The Investigator will be provided with an Investigator's file at the start of the study. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study.

It is the responsibility of the Investigator to ensure that the patient identification sheets are stored according the ICH-GCP and European Union Directive 2002/58/EC (see Section 21). All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the Investigator will notify the Sponsor.

18.6 Monitoring, Quality Assurance, and Inspection by Authorities

This study is to be conducted in accordance with ICH E6. The appointed clinical monitor will arrange regular visits to the trial centre(s) to check progress with the study and to collect completed CRFs.

During monitoring visits, the monitors will:

- Help resolve any problems
- Examine all CRFs for omission of data, compliance and possible AEs
- Discuss inconsistencies in the trial data
- Ensure that all trial materials are correctly stored and dispensed
- Check adherence to the obligations of the Investigator
- Review consent forms, in particular the date of consent and signature
- Perform source data verification as described below

In line with ICH E6, monitoring will include verification of data entered in the CRF against original patient records. This verification will be performed by direct access to the original patient records, and the Sponsor guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification.

In addition, the representatives of the Sponsor's Quality Management department, their appointed monitoring organisations, and regulatory authorities are permitted to inspect the study documents (study protocol, CRFs, IMP, original medical records/files). All patient data shall be treated confidentially.

In the course of the clinical study, the CRFs shall be forwarded to the Sponsor after completion of the individual sections (e.g., visits) of the study. The study protocol, each step of the data-recording procedure, and the handling of the data as well as the study report shall be patient to the review of the Sponsor's independent clinical Quality Management department. Audits can be conducted to assure the validity of the study data.

18.7 Completing, Signing, and Archiving CRFs

All materials or supplies provided by the Sponsor will be returned to the Sponsor upon study completion. The Investigator will notify the EC when the study has been completed.

The Investigator must keep a separate patient identification list showing code numbers, names, and dates of birth to allow unambiguous identification of each patient included in the study. A note will be made in the hospital medical records that the patient is participating in a clinical study. The CRF will be completed legibly in black ball-point pen, with reasons given for missing data.

The statement on the last page of the CRF will be signed by the Principal Investigator. Any used supplemental page will be signed by the Investigator. Corrections to the data will be made in a manner that does not obscure the original entry and will be dated and initialled by the Investigator or assigned designee.

Because it is extremely important to have proper data collection in a timely manner, the Investigator shall complete the CRFs and continually deliver them to the monitor. When the monitor requests additional data or clarification of data for the CRF, the request must be answered satisfactorily before the next monitoring visit.

18.8 Data Management and Data Control

The Sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the Sponsor's SOPs for clinical studies.

Source data, source documents, CRFs, copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the Investigator/institution when these documents need no longer to be retained.

The original CRFs will be archived by the Sponsor for the lifetime of the product. No study document or image should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice should be given to the Sponsor.

19. FINANCING AND INSURANCE

A separate financial agreement (Clinical Investigators' Agreement) will be made between each Principal Investigator and the Sponsor before the investigational product is delivered.

PARI Pharma GmbH has insurance coverage for study related IMP-induced injury and other liabilities incurred during clinical studies which will provide compensation for any study related injury according to the guidelines set out by the Association of the British Pharmaceutical Industry (ABPI), namely “Clinical Studies Compensation for Medicine Induced Injury”.

20. REPORTING AND PUBLICATION OF RESULTS

After conclusion of the study, an integrated clinical and statistical study report shall be written by the Sponsor or designee in consultation with the coordinating Investigator. The first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by Investigators or their representatives will require pre-submission review by the Sponsor. The Sponsor is entitled to delay publication in order to obtain patent protection. For more details regarding publications, refer to the clinical study agreement/Investigator study agreement.

The final report will be signed by the Sponsor and the Principal Investigator with the highest recruitment of evaluable patients.

The result of the study will be published and/or presented in scientific meetings in a timely manner. Any formal publication of study will be a collaborative effort between the Sponsor and the Investigator(s). All manuscripts and abstracts will be reviewed and approved in writing by the Sponsor prior to submission.

Policies regarding the publication of the study results are defined in the clinical Investigator's agreement.

21. ARCHIVING AND DATA RETENTION

All study documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with the European Union Directive 2002/58/EC. These documents should be retained for a longer period however, if required by regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

The final database will be archived by the Sponsor according to regulatory requirements.

22. REFERENCES

1. Armengot M, Juan G, Barona R, et al. Immotile cilia syndrome. Nasal mucociliary function and nasal ciliary abnormalities. *Rhinology* 1994; 32:109-111.
2. Baraniuk J, Maibach H. Pathophysiological classification of chronic rhinosinusitis. *Respir Res* 2005; 6:149.
3. Bhattacharyya T, Piccirillo J, Wippold FJ. Relationship between patients-based descriptions of sinusitis and paranasal sinus computed tomographic findings. *Arch Otolaryngol Head Neck Surg* 1997; 123:1189-92.
4. Clement PA. Definitions of sinusitis. *Acta Otorhinolaryngol Belg* 1997; 51:201-3.
5. Fokkens W, Lund V, Mollol J, *et al*. The European Position Paper of Rhinosinusitis and Nasal Polyps (EP3OS) group. *Rhinology* 2007; 45, Suppl. 20:1-137.
6. Hopkins C, Browne DW, Slack R, *et al*. The Lund-Mackay staging system for chronic rhinosinusitis: How is it used and what does it predict? *Otolaryngol Head Neck Surg* 2007; 137: 555-561.
7. Lund VJ, Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. *Ann Otol Rhinol Lanryngol Suppl* 1995; 167:17-21.
8. Mainz J, Mentzel HJ, Schneider G, *et al*. Sinu-nasal inhalation of Dornase alfa in CF. Results of a double-blind placebo-controlled pilot trial. *J Cystic Fibrosis* 2008; 7:S27.
9. Min YG, Shin JS, Choi SH, *et al*. Primary ciliary dyskinesia. Ultrastructural defects and clinical features. *Rhinology* 1995; 33:189-193.
10. Möller W, Schuschnig U, Meyer G, *et al.* Ventilation and drug delivery to the paranasal sinuses: studies in a nasal cast using pulsating airflow. *Rhinology* 2008; 46.
11. Möller W, Schuschnig U, Meyer G, *et al.* Ventilation and aerosolized drug delivery to the paranasal sinuses using pulsating airflow – a preliminary study. *Rhinology* 2009; 47:405-412.
12. Möller W, Schuschnig U, Saba GK, *et al.* Pulsating aerosols for drug delivery to the sinuses in healthy volunteers. *Otolaryngology-Head and Neck Surgery* 2010; 142: 382-388.
13. Piccirillo J, Edwards D, Haiduk A, *et al*. Psychometric and clinimetric validity of the 31-item Rhinosinusitis Outcome Measure (RSOM-31). *Am J Rhinol* 1995; 9:297-306.
14. Sato Y, Hyo N, Sato M, *et al*. Intra-nasal distrubition of aerosols with or without vibration. *Z Erkr Atmungsorgane* 1981; 157:276-280.
15. Stewart MH, Sicard MW, Piccirillo FJ, *et al*. Severity staging in chronic sinusitis: are CT scan findings related to patient symptoms? *Am J Rhinol* 1999; 13:161-7
16. Van Cauwenberge P, Watelet JB. Epidemiology of chronic rhinosinusitis. *Thorax* 2000; 55:20S-1.

17. Wabnitz DA, Nair S, Wormald PJ. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. *Am J Rhinol* 2005; 19:91-6.

23. APPENDIX I – CORE INFORMED CONSENT FORM

The informed consent form must be adapted to local requirements but must contain at least the following points:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The patient's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the patient and, when applicable, to an embryo, foetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the patient, the patient should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
- The compensation and/or treatment available to the patient in the event of trial related patient injury.
- The anticipated prorated payment, if any, to the patient for participating in the trial.
- The anticipated expenses, if any, to the patient for participating in the trial.
- That the patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient is otherwise entitled.
- That the monitor(s), the auditor(s), the EC, and the regulatory authority(ies) will be granted direct access to the patient‘s original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the patient or the patient‘s legally acceptable representative is authorizing such access.
- That records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
- That the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient‘s willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial patients, and whom to contact in the event of trial-related injury.

- The foreseeable circumstances and/or reasons under which the patient's participation in the trial may be terminated.
- The expected duration of the patient's participation in the trial.
- The approximate number of patients involved in the trial.

24. APPENDIX II – ACCEPTABLE METHODS OF CONTRACEPTION

According to the EMEA guideline 286/95, the following methods are allowed for contraception during the clinical trial with a failure rate of less than 1%:

- contraceptive implant
- injectable or patch hormone therapy
- combine oral contraceptives and barrier methods
- intrauterine device (IUD)
- sexual abstinence
- surgical sterilisation of the female or male partner

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of the study, the patient must be withdrawn from all IMP treatment immediately. The Investigator should report pregnancy cases occurring during the clinical trial to SGS Life Science Services Medical Affairs immediately using the SAE form. PARI Pharma GmbH must be notified without delay. Pregnancy cases will be followed-up during the entire course of the pregnancy and postpartum period using SGS Life Science Services Drug Exposure during Pregnancy – Pregnancy Form A and End of Pregnancy – Pregnancy Form B. Parental and neonatal outcomes must be recorded even in they are completely normal and without AEs. The SAE reporting procedure should be followed, even though pregnancy is not considered a SAE. No “serious criterion” should be checked. The SAE report form is solely used to ensure expedited reporting.