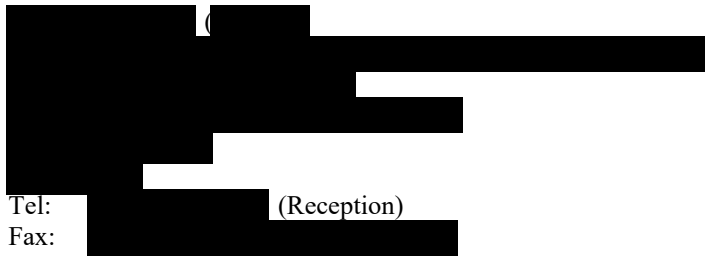
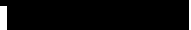




Clinical Trial Protocol

Document Number:		c11001605-04
EudraCT No.: EU Trial No.:	Not applicable	
BI Trial No.:	1024.9	
BI Investigational Product(s):	Ibuprofen and Pseudoephedrine	
Title:	Bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl compared to two film coated fixed dose combination tablets RhinAdvil® (200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) administered in at least 48 healthy male and female subjects (Open-label, randomized, laboratory blind, single dose, two-way crossover, Phase I trial).	
Lay Title:	Bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl compared to two film coated fixed dose combination tablets RhinAdvil®(200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) administered in healthy subjects.	
Clinical Phase:	I	
Trial Clinical Monitor:	<div style="background-color: black; width: 150px; height: 15px; margin-bottom: 5px;"></div> on behalf of: <div style="background-color: black; width: 480px; height: 15px; margin-bottom: 5px;"></div> Phone: <div style="background-color: black; width: 150px; height: 15px; display: inline-block;"></div> Fax: <div style="background-color: black; width: 150px; height: 15px; display: inline-block;"></div>	
Principal Investigator:	<div style="background-color: black; width: 550px; height: 20px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 650px; height: 20px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 260px; height: 20px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 150px; height: 20px; margin-bottom: 5px;"></div> Tel: <div style="background-color: black; width: 150px; height: 15px; display: inline-block;"></div> (Reception) Fax: <div style="background-color: black; width: 250px; height: 15px; display: inline-block;"></div>	
Status:	Final Protocol (Revised Protocol based on Global Amendment 01)	
Version and Date:	Version:	Date:
	3.0	20 February 2017
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		N/A	
Name of active ingredient:		Ibuprofen and Pseudoephedrine	
Amended Protocol date: 30 January 2017	Trial number: 1024.9		Revision date: 20 February 2017
Title of trial:	Bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl compared to two film coated fixed dose combination tablets RhinAdvil® (200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) administered in at least 48 healthy male and female subjects (Open-label, randomised, laboratory blind, single dose, two-way crossover, Phase I trial).		
Principal Investigator:	 Tel:  (Reception) Fax: 		
Trial site(s):	Bloemfontein Early Phase Clinical Unit, PAREXEL International (South Africa)		
Clinical phase:	I		
Objectives:	Primary objective: To demonstrate the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to the analytes, ibuprofen and pseudoephedrine. Secondary objective: To assess the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to R- and S-ibuprofen (enantiomers of ibuprofen).		

Name of company:		Boehringer Ingelheim	
Name of finished product:		N/A	
Name of active ingredient:		Ibuprofen and Pseudoephedrine	
Amended Protocol date: 30 January 2017	Trial number: 1024.9		Revision date: 20 February 2017
Methodology:	Open-label, randomised, single dose, two-way crossover design		
No. of patients:	Fifty-six eligible subjects will be entered into the study, to complete with no less than 48 evaluable subjects (no less than 16 of each gender).		
Total entered:	56		
Diagnosis:	Not applicable		
Main criteria for inclusion:	Healthy male and female subjects, age ≥ 21 and ≤ 50 years, BMI range: ≥ 18.5 and ≤ 29.9 kg/m ² . Minimum of 1/3 of each gender should complete the study. Signed informed consent of the subject according to the present law.		
Test product(s):	Fixed dose combination 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl film-coated tablet		
Dose:	400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl		
Mode of administration:	Oral administration with 240 mL water in standing position after an overnight fast of at least 10 hours		
Comparator products:	2 tablets containing Fixed Dose combination RhinAdvil® (200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl)		
Dose:	200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl		

Name of company:		Boehringer Ingelheim	
Name of finished product:		N/A	
Name of active ingredient:		Ibuprofen and Pseudoephedrine	
Amended Protocol date: 30 January 2017	Trial number: 1024.9		Revision date: 20 February 2017
Mode of administration:	Oral administration with 240 mL water in standing position after an overnight fast of at least 10 hours		
Duration of treatment:	Single dose in each treatment period separated by a wash-out phase of at least 5 days		
Endpoints	<p>Primary endpoints: AUC_{0-tz} and C_{max} of ibuprofen and pseudoephedrine-HCl in plasma</p> <p>Secondary endpoints: AUC_{0-∞} of ibuprofen and pseudoephedrine-HCl in plasma; AUC_{0-tz}, AUC_{0-∞} and C_{max} of R-ibuprofen and S-ibuprofen in plasma; and S/R-ibuprofen ratio for AUC_{0-tz} (i.e., AUC_{0-tz} S-ibuprofen / AUC_{0-tz} R-ibuprofen) of R- ibuprofen and S-ibuprofen in plasma</p> 		
Safety criteria:	Physical examination, vital signs (BP, PR), 12-lead ECG, laboratory tests, adverse events, tolerability assessment		
Statistical methods:	<p>The assessment of bioequivalence will be based upon two-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary and secondary endpoints using an acceptance range of 80.00-125.00%. This method is equivalent to the two one-sided t-tests procedure, each at the 5% significance level. The statistical model will be an ANOVA on the logarithmic scale including effects for 'sequence', 'subjects nested within sequences', 'period' and 'treatment'. CIs will be calculated based on the residual error from ANOVA.</p> <p>Descriptive statistics will be calculated for all endpoints.</p>		

FLOW CHART

	Visit	Day	Planned time [h:min]	Clock time of actual day [h:min] ¹	Event and comment	Blood sampling for PK ⁸	Laboratory tests	ECG	Vital Signs ⁹	Recording AEs / concomitant therapy		
Screening	1	-21 to -1			Screening examination ^{2, 5}		x ^{5 & 7}	x	x	X		
Treatment period ⁴ 1 or 2	2 or 3 ⁴		-11:50 until 0:00	20:30 until 0:00	Admission to trial center, Pregnancy test	x	x ⁶		x	X		
		1	0:00	8:00	Study drug administration					X		
			0:10	8:10		x				X		
			0:20	8:20		x				X		
			0:30	8:30		x			x	X		
			0:45	8:45		x				X		
			1:00	9:00		x				X		
			1:15	9:15		x				X		
			1:30	9:30		x				X		
			1:45	9:45		x				X		
			2:00	10:00		x		x		X		
			2:30	10:30		x				X		
			3:00	11:00		x			x	X		
			4:00	12:00		Lunch	x				X	
			6:00	14:00			x				X	
			8:00	16:00		Snack	x				X	
			10:00	18:00		Dinner	x				X	
				12:00	20:00		x				X	
				2	24:00	8:00		x				X
					30:00	14:00	Discharge from trial centre	x				X
End of study	4				End-of-study examination ³		x ⁵	x	x	X		

- 1 Actual clock time depends on the time of dosing.
- 2 Screening will occur within 21 days before first drug administration and will include subject information, informed consent, demographics, vital signs, physical examination, ECG, determination of the body height and weight, smoking and alcohol history, medical history, concomitant medication, laboratory and review of inclusion and exclusion criteria.
- 3 End-of-study examination to be performed within 7 days of last study drug administration or if the subject was withdrawn or withdrew from the study but not earlier than last PK sampling, including physical examination, vital signs, ECG, laboratory, pregnancy test, concomitant medication, and review of adverse events.
- 4 Two identical treatment periods with an interval of at least 5 days between drug administrations.
- 5 Clinical chemistry, haematology, urinalysis, pregnancy test.
In addition at visit 1: drug screening, serology (HBV, HCV, HIV), and alcohol breath test.
- 6 Baseline: Only substrates, haematology and enzymes. Baseline assessments are done for safety reasons.
- 7 On admission for treatment period 1 and 2: alcohol breath test, and urine pregnancy test.
- 8 Time interval allowance for the PK sampling: 0-1 hours: ± 2 min; 1-8 hours: ± 5 min; 8-30 hours: ± 15 min.
- 9 Vital signs: Body temperature only at screening and pre dose.

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline Phosphatase
AST	Aspartate transaminase (SGOT)
AUC _{0-∞}	Area under the concentration-time curve of the analyte in plasma from 0 hours extrapolated to infinity
AUC _{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLQ	Below the limit of quantification
BMI	Body Mass Index (weight divided by height squared)
BP	Blood Pressure
C _{max}	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical Research Associate
CRF	Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
eCRF	eCRF Electronic Case report form: PAREXEL data capture system ClinBase™
ECG	Electrocardiogram
EDTA	Ethylendiaminetetraacetic acid
FAS	Full Analysis Set
FC	Flow Chart
FDC	Fixed dose combination
G-6-PD	Glukose-6-phosphat-dehydrogenase
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl-transferase (GGT)
gCV	Geometric coefficient of variation
gMean	Geometric Mean
HBV	Hepatitis B virus
HCl	Hydrochloric acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International committee on harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine device
λ _z	Terminal rate constant of the analyte in plasma
LDH	Lactic-dehydrogenase

ln	Natural logarithm
LoEE	List of Essential Element
MedDRA	Medical Dictionary for Drug Regulatory Activities
N	Number
NC	Not calculated
NOA	Not analysed
NOR	No valid result
NOS	No sample available
NSAID	Nonsteroidal anti-inflammatory drug
OPU	Operative Unit
pH	Pondus hydrogenii; negative logarithm of the hydrogen ion concentration
PK	Pharmacokinetics
p.o.	per os (oral)
PR	Pulse rate
R	Reference treatment SAE
	Serious Adverse Event
SGAE	Significant adverse event
T	Test treatment

	in plasma
TCM	Trial Clinical Monitor
TMF	Trial Master File
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The common cold remains the most prevalent cause of acute morbidity. The cause is a viral infection, mostly by rhinovirus (up to 80%), corona virus (10-15%), parainfluenza (5%) or respiratory syncytial virus (5%) ([R13-2920](#)).

Looking at the typical course of a common cold it mostly starts with sore throat, followed by the simultaneous occurrence of rhino sinusitis and headache and/or muscle ache. While these symptoms gradually resolve, a dry cough may occur. In a later stage, the dry cough will develop into cough accompanied by thick tenacious secretion.

As the common cold is a disease of viral origin and usually benign in nature, symptomatic treatment is currently the mainstay in the therapy ([P88-35100](#)).

Different products are available on the market to treat the single symptoms such as:

- Nasal decongestants against nasal congestion
- Analgesics against headache, pain and fever
- Antihistamines with a drying effect on the nasal passages and a decrease in sneezing
- Cough suppressants against dry cough
- Mucolytics and secretolytics against productive cough.

Symptomatic treatment with several individual non-prescription products may be inconvenient and present a significant additional cost to the patient. Indeed, in a survey in 250 community pharmacists in five European countries, 60% of the questioned pharmacists said that they preferred to treat themselves with a combination-product when suffering from a common cold ([P97-6591](#)).

Most symptoms of common cold are present sometime during the course of the cold, they appear, peak and resolve at different times. Nasal congestion and headache or muscle ache are often concurrent and both are considered as being bothersome by the patient.

Therefore the development of a fixed dose combination product of an analgesic and a nasal decongestant for the treatment of both concurrent and most bothersome symptoms was considered.

The combination of an analgesic and a decongestant for treatment of the symptoms associated with the common cold is based on the rationale of relief from inflammation-based symptoms and nasal congestion.

Ibuprofen has been in therapeutic use for decades as nonsteroidal anti-inflammatory drug (NSAID). Pseudoephedrine has been in therapeutic use for decades as decongestant, respectively.

Their combination provides the cold and influenza sufferer with a convenient and effective treatment for the relief of their symptoms ([P10-06083](#)).

Based on positive experience with free combination of both compounds also fixed dose combination products with 200 mg ibuprofen and 30 mg pseudoephedrine-HCl have been developed and introduced into the European market.

In 2005 a mutual recognition process was granted with France as reference member state and Germany, Austria and Luxembourg as concerned member states. Local registrations were granted in UK in the 1990ies and Poland in 2004.

A fixed dose combination (FDC) product containing 400 mg ibuprofen free acid and 60 mg pseudoephedrine-HCl per film-coated tablet is going to be developed. This product should be registered via a decentralised procedure and marketed throughout Europe.

1.2 DRUG PROFILE

Ibuprofen

Ibuprofen is a NSAID of the arylpropionic acids class. This non-selective cyclooxygenase inhibitor exhibits marked stereo selectivity in pharmacokinetics (inversion, elimination) and pharmacodynamics, as the S-(+) enantiomer is considerably more potent and formed by unidirectional inversion of the R-(-)-enantiomer.

Main indications are the treatment of mild to moderate pain from various origins, in particular in the therapy of osteo-arthritis, rheumatoid arthritis and soft-tissue disorders. In addition, antipyretic activity and short time inhibition of platelet aggregation were observed.

Absorption occurs rapidly and completely after oral administration. Absolute bioavailability is almost 100%. Individual peak plasma concentrations are observed within three hours after administration of the free acid, with mean values reported as one to two hours. Rate of absorption, and thus maximum plasma concentrations (C_{max}), may be significantly influenced by formulation properties while total exposure (AUC) remains unaffected. The apparent volume of distribution is 0.1 to 0.2 L/kg. As this value approximates plasma volume, it is suggested that plasma protein binding (> 98%) is preferred to tissue binding.

Following oral administration, about 80% of an ibuprofen dose is recovered as hydroxyl- and carboxy-metabolites, either conjugated or unconjugated, in the urine within 24 hours. Only about 10% is found in the faeces. The major metabolic pathway involves CYP 2C9 and probably CYP 2C8. Most important metabolites are 2-hydroxy- and carboxy-ibuprofen while 1- and 3- hydroxy-ibuprofen were found in only very small concentrations. No pharmacologically active metabolite is known.

Pharmacokinetics of ibuprofen is dose dependent. At doses greater than 600 mg, the unbound fraction of the drug increases, probably due to saturation of the protein binding, resulting in an increased clearance and less than proportional area under the curve. Mean terminal elimination half-life is reported as 2 hours. ***For additional information please refer to RhinAdvil® Summary of Product Characteristics.*** Evidence for accumulation or time dependency of pharmacokinetics after multiple dosing was not found.

There are some concerns about the use of NSAIDs. Much of these concerns are related to long-term therapy with higher doses in special indications such as e.g. rheumatoid arthritis. Ample safety data is available for indications other than upper respiratory tract infections. However, this data will not be addressed here in detail. One of the few studies providing safety information on the use of ibuprofen in the treatment of cold and flu symptoms was reported recently.

In a double-blind randomised study, the tolerability of ibuprofen (up to 1.2 g daily), acetylsalicylic acid and acetaminophen (both up to 3 g daily) was investigated in 2815 patients with mild to moderate pain resulting from cold/flu symptoms or sore throat for seven days. The main outcome was the rate of significant adverse events (SGAE). Rates of SGAE for ibuprofen, acetylsalicylic acid and paracetamol were respectively 12.0%, 15.7% and 12.3%. Ibuprofen was significantly better tolerated than acetylsalicylic acid ($p=0.02$) and showed comparable tolerability compared to paracetamol. The latter was also true for total digestive system events and for abdominal pain and dyspepsia. For all other adverse events the results were consistent with SGAEs, i.e. comparable proportions of patients in the ibuprofen and paracetamol groups and higher percentages of patients in the acetylsalicylic acid group than in the ibuprofen group. In conclusion patients with mild to moderate pain resulting from cold/flu symptoms or sore throat, ibuprofen used in over-the-counter is well tolerated ([P04-01312](#)).

Ibuprofen has an excellent safety profile in multiple-dose use with a frequency of gastrointestinal adverse events comparable to placebo.

Pseudoephedrine

Pseudoephedrine is a natural alkaloid, commonly manufactured by yeast fermentation. This sympathomimetic drug exhibits weak agonist activity at α - and β -adrenergic receptors and initiates release of endogenous norepinephrine from storage vesicles in presynaptic neurons. Thus, it is used as decongestant of mucous membranes.

The compound is rapidly and completely absorbed after oral administration with peak plasma concentrations occurring within 20 to 120 minutes. No information is available on plasma protein binding of pseudoephedrine, the apparent volume of distribution is reported as 2 – 3.3 L/kg.

Pseudoephedrine is metabolised in the liver, but only to a small extent. Main metabolite is the pharmacologically active nor-pseudoephedrine. Between 70 and 90% of a given dose is excreted unchanged in the urine, only 1% as nor-pseudoephedrine.

Mean terminal elimination half-life is reported between five and six hours, individual values of up to 8 hours have been observed ([R09-2316](#)). Obviously, pH of the urine exhibits certain impact on urinary excretion with normal values at pH of 5 to 6. Higher and lower pH-values may increase or decrease half-life significantly due to changes in solubility and tubular reabsorption.

In a meta-analysis of 2 repeated dose studies using pseudoephedrine for the symptomatic treatment of the common cold, no overall differences in the risk of adverse events compared

to placebo have been shown ([R07-2230](#)).

For further detailed information, please refer to the (RhinAdvil® Summary of Product Characteristics)

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Ibuprofen and pseudoephedrine are being used therapeutically for decades as NSAID and decongestant, respectively.

Also combinations of pseudoephedrine with NSAID or antihistamines are common.

Based on positive experience with free combination of both compounds, also fixed dose combination products with 200 mg ibuprofen and 30 mg pseudoephedrine-HCl have been developed and introduced into the market in some European countries.

Marketing Authorisation Application in the EU is planned for a fixed dose combination product as film coated tablets containing 400 mg of ibuprofen and 60 mg of pseudoephedrine as the test product.

Bioequivalence to RhinAdvil® as reference product, an approved and marketed product in France, Germany, (in the past also in Austria, Belgium and Luxembourg) will be assessed by means of a clinical phase I study.

Rationale of the study is to establish bioequivalence of the test product to the reference product.

2.2 TRIAL OBJECTIVES

2.2.1 Primary objective

To demonstrate the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to the analytes, ibuprofen and pseudoephedrine.

2.2.2 Secondary objective

To assess the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to R- and S-ibuprofen (enantiomers of ibuprofen).

2.3 BENEFIT – RISK ASSESSMENT

Participation in this bioequivalence study is without any therapeutic benefit for the healthy subjects. Their participation in the study, however, is of importance for the development of a new oral fixed dose combination of nonsteroidal anti-inflammatory drug (NSAID) and decongestant containing Ibuprofen 400 mg and Pseudoephedrine 60 mg.

The subjects are exposed to:

- the risks of the study procedures
- the known risks related to the exposure with the study medication

The use of an indwelling cannula for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to vein puncturing for further blood sampling. In rare cases a nerve might be injured while inserting the cannula. This could be followed by paresthesia, reduced sensibility or pain for a long-term period.

The total volume of blood withdrawn during the entire study will be about ~ 362.5 ml. No safety related risk is expected from this blood withdrawal.

Drug related risks

Ibuprofen:

Reported main side effects of Ibuprofen are:

Agranulocytosis, haemolytic anaemia, dysopia, dyspepsia, epigastralgia, gastrointestinal bleeding, impaired gastrointestinal motility, nausea, vomiting, oedema, hypersensitivity, aseptic meningitis, increased levels of transaminase, dizziness, headache, renal dysfunction, oliguria, asthma, progression of chronic urticaria, pruritus, skin eruption, rash, erythema multiforme, angioedema.

Pseudoephedrine:

Reported main side effects of pseudoephedrine-HCl are:

Palpitations, tachycardia, narrow-angle glaucoma, dry mouth, nausea, vomiting, rare cases of haemorrhagic stroke, headache, **convulsion***, anxiety, **restlessness***, **abnormality in behaviour***, **hallucinations***, dysuria, retention of urine, sweating, exanthema, pruritus, urticaria, hypertony

*have been reported rarely, particularly in children

For further detailed information, please refer to the (RhinAdvil® Summary of Product Characteristics)

Overall Risk – Benefit assessment

Overall the risk for subjects participating in this trial is considered to be low and acceptable. Because of the anticipated benefit that a successful clinical development of the film coated fixed dose combination tablet containing ibuprofen 400 mg and pseudoephedrine-HCl 60 mg (Test Product) could provide patients a respectable amount of release of the symptoms associated with common cold. The sponsor feels the benefit of a successful clinical development of one film coated fixed dose combination tablet to outweigh the risk.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, single dose, randomised, laboratory blind, two-way crossover trial.

The following treatments will be administered in the fasting state:

Test (T): Film coated fixed dose combination tablet containing
Ibuprofen 400 mg and Pseudoephedrine 60 mg

Reference (R): **RhinAdvil®** two fixed dose combination tablets containing
Ibuprofen 200 mg and Pseudoephedrine 30 mg

The two treatment sequences T-R and R-T will be randomly allocated to the subjects.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

The conduct of the study will be monitored by a representative of the Sponsor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

Safety Reporting will be done according to BI SOPs and will be described further in [Section 5.3.6.2](#).

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined in accordance with PAREXEL standard procedures.

A local laboratory service will be used in this trial. Procedures will be in accordance with PAREXEL standard procedures. Tests not performed by the local laboratory will be outsourced to PAREXEL's preferred vendor laboratory for analysis. The results from the preferred vendor laboratory will be transmitted to ClinBase™ and electronically transferred to Data Management.

Data Management and Statistical Evaluation will be done according to PAREXEL standard procedures. PK Analysis will be done according to non-compartmental analyses guidance and the TSAP.

A list of SOPs will be contained in the ISF.

A list of responsible persons and relevant local information will be contained in the ISF.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

For bioequivalence studies, the crossover design is viewed favourably due to its efficiency: since each subject serves as his own control, the comparison between treatments is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between treatments [R94-1529].

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of the analytes, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 56 healthy male and female subjects will be randomised in the study, to complete with at least 48 evaluable subjects. At least 16 of each gender should be included in the evaluable population. Subjects will be recruited from the subjects' pool of Bloemfontein Early Phase Clinical Unit, PAREXEL International (South Africa).

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

Please refer to [Section 8.3.1](#) (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

- 1 Healthy males and females according to the following criteria:
- 2 Based upon a complete medical history, including physical examination, vital signs (BP, PR), 12-lead ECG, clinical laboratory tests
- 3 Age ≥ 21 to ≤ 50 years
- 4 Minimum weight 50kg – both males and females
- 5 BMI ≥ 18.5 to ≤ 29.9 kg/m²
- 6 Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial
- 7 Male or female patients. Women of childbearing potential¹ must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly e.g. implants, injectables,

¹ Women of childbearing potential are defined as:

- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and not permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

combined hormonal contraceptives, intrauterine device, or surgical sterilisation (including hysterectomy). In addition to this, also a barrier method (e.g. male condom) will be required, if the female is not surgically sterilised. A list of contraception methods meeting these criteria is provided in the patient information. Abstaining from sexual activity (if this is the usual lifestyle of the subject) is considered an acceptable method of birth control.

3.3.3 Exclusion criteria

- 1 Any finding of the medical examination (including BP, PR and ECG) deviating from normal and of clinical relevance at the discretion of the investigator
- 2 Any evidence of a clinically relevant concomitant disease
- 3 Any relevant Gastrointestinal (e.g. ulcera, hernia, bleedings and spasm), hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
- 4 Any relevant surgery of the gastrointestinal tract (except appendectomy)
- 5 Diseases of the central nervous system (such as epilepsy) or psychiatric disorders or relevant neurological disorders at the discretion of the investigator
- 6 History of relevant orthostatic hypotension, fainting spells or blackouts
- 7 Chronic or relevant acute infections
- 8 History of relevant allergy or hypersensitivity (including allergy to drug or its excipients) as judged clinically relevant by the investigator
- 9 Intake of drugs with a long half-life (>24 hours) within at least 1 month or less than 10 half-lives of the respective drug prior to first drug administration
- 10 Use of drugs which might reasonably influence the results of the trial based on the knowledge at the time of protocol preparation within 14 days prior to randomisation
- 11 Participation in another trial with an investigational drug within 2 months prior to administration or during the trial
- 12 Smoker (>10 cigarettes or >3 cigars or >3 pipes/day)
- 13 Inability to refrain from smoking on trial days as judged by the investigator
- 14 Alcohol abuse (average consumption of more than 2 units per day for females and more than 3 units per day for males)
- 15 Drug abuse
- 16 Blood donation (more than 100 mL within four weeks prior to administration of the trial drug in this study)
- 17 Excessive physical activities within 1 week prior to randomisation or during the trial
- 18 Any laboratory value outside the reference range that is of clinical relevance at the discretion of the investigator
- 19 Inability to comply with dietary regimen of the study centre
- 20 Unwilling to avoid excessive sunlight exposure
- 21 Use of drugs which might reasonably influence the results of the trial or that prolong the QT/QTc interval within 14 days prior to administration or during the trial, and CYP2C8 substrates such as amiodarone, amodiaquine, paclitaxel, rosiglitazone, pioglitazone and repaglinide or CYP2C9 such as warfarin, tolbutamide, phenytoin, losartan,
- 22 A marked baseline prolongation of the QTc B interval (e.g., repeated demonstration of a QTc B interval >450 ms)

- 23 A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalaemia, family history of Long QT Syndrome)

Special exclusion criteria:

- 24 Subjects with history of bronchospasm, rhinitis or urticaria associated with NSAID - Asthma
- 25 Risk of or manifested narrow-angle glaucoma
- 26 Risk of urinary retention due to urethro-prostatic diseases / prostatic enlargement
- 27 Subjects with the rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase isomaltase deficiency
- 28 Regular treatment with any systemically available medication (except hormonal contraceptives and hormonal replacement therapy e.g. estrogens, L-thyroxine)
- 29 Subjects, who report a frequent occurrence of migraine attacks

For female subjects of childbearing potential only:

30. Positive pregnancy test, pregnancy or planning to become pregnant during the study or within 2 months after study completion
- 31 No adequate contraception during the study including three months before first dosing until 2 month after study completion.
- 32 Lactation

Administrative reasons:

- 33 Subjects suspected or known not to follow instructions
- 34 Subjects who are unable to understand the written and verbal instructions, in particular regarding the risks and inconveniences they will be exposed to during their participation in the study

The exclusion criteria are chosen to assure that subjects with specific risks for administration of the investigational medicinal products and subjects with conditions, which may have an impact on pharmacokinetic parameters, cannot be included

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

Trial criteria:

The trial as a whole will be terminated prematurely if:

New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment

Subject criteria:

An individual subject is to be withdrawn from the trial if:

The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision

The subject has to take any concomitant drugs interfering with the study medication

The subject is no longer able to participate for other medical reasons (e.g. pregnancy, surgery, adverse events or other diseases)

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

A subject can also be removed from the trial, if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the electronic case report form (eCRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the eCRF; in addition, the data will be included in the eCRF/trial database and will be reported in the CTR. At the time of discontinuation, a complete end-of-trial examination will be performed, if possible, and the information will be recorded in the eCRF. If the discontinuation occurs shortly after administration, the discontinued subject should be evaluated for AEs and concomitant therapies if possible as long as measurable drug levels are still likely to be present, assuming the subject agrees to such an evaluation.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR.

3.3.4.2 Replacement of subjects

Subjects who withdraw or are withdrawn from the study will not be replaced, unless fewer complete the study than the estimated number of evaluable subjects.

If a subject is replaced, the replacement will be allocated the subject number of 500 plus the subject number being replaced (e.g., Subject ■ will be replaced by ■). The subject numbers being replaced will be selected such that the replacement subjects receive the same treatment sequence as the withdrawn subjects and the sequence balance is maintained.

Replacement subject must preferably be of the same gender as the withdrawn subjects, if this is needed to secure the requirement that at least 1/3 of each gender should complete the study.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- 1 Failure to meet expected enrolment goals overall or at a particular trial site
- 2 Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- 3 Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

The Investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are described below.

Substance:	Ibuprofen+Pseudoephedrine-HCl
Pharmaceutical form:	Fixed dose combination film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	400 mg Ibuprofen, 60 mg Pseudoephedrine-HCl
Posology:	1-0 (1 tablet in each treatment period)
Route of administration:	oral
Manufacturer:	Przedsiębiorstwo Produkcji Farmaceutycznej Hasco – Lek
Country of Origin:	Poland

The characteristics of the reference products are described below. Substance:

	Ibuprofen+Pseudoephedrine-HCl (RhinAdvil®)
Pharmaceutical form:	Fixed dose combination tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	200 mg Ibuprofen, 30 mg Pseudoephedrine-HCl
Posology:	2-0 (2 tablets, single dose, in each treatment period)
Route of administration:	oral
Manufacturer:	Pfizer Consumer Manufacturing Italy, Via Nettunese 90, 04011 Aprilia, Italy
Country of Origin:	Italy

4.1.2 Selection of doses in the trial

The doses selected for this trial are fully in line with already registered products.

4.1.3 Method of assigning subjects to treatment groups

This trial is a two-way crossover study. Subjects will receive either the test or reference products, according to the randomisation schedule.

The randomisation schedule will be provided by PAREXEL Biostatistics. The randomisation schedule will be generated utilizing the PROC PLAN procedure of SAS® software.

The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication, without any exposure of the subjects to the randomisation list (i.e. subjects will not select study subject numbers on basis of treatment sequence). Subjects will be assigned randomisation numbers [REDACTED] sequentially. Possible replacements will be handled according to [Section 3.3.4.2](#).

Subjects then will be randomised to one of two treatment sequences (RT or TR) using the

randomisation schedule.

Blinding is described in [Section 4.1.5.1](#).

4.1.4 Drug assignment and administration of doses for each patient

The study drugs will be administered in the morning of day 1 between usually 07:30 and 10:00 hours clock time. After an overnight fast of at least 10 hours, the medication will be administered as a single oral dose together with 240 mL water in the standing position under supervision of the investigating physician or an authorised designee. Subjects will be kept under close medical surveillance for the duration of the in-house period and are not allowed to lie down during the 2 hours following drug administration. Subjects will remain fasted until at least 4 hours after drug intake. Water will be allowed except 1 hour before to 2 hours after drug administration. Standardised meals will be served in each period of the study.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label, laboratory-blind study. Access to the randomisation schedule will be restricted to assigned study staff members of PAREXEL Biostatistics and PAREXEL Pharmaceutical Services, as well as the PI and designee. Study staff members of the laboratories of BASD are not allowed access to the randomisation schedule until after statistical analysis of the study results. The final statistical analysis will be done according to the Statistical Analysis Plan (SAP) and will be based on data following database lock.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. The clinical trial supply consists of containers with trial- and site identification that hold the trial medication.

The containers will be labelled with the required information according to the German Drug Law (16. AMG Novelle) as well as Annex 13/EU-GMP.

Smaller boxes in the clinical trial supply containers are labelled with:

- Trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration: According to the protocol
- Term "for clinical trial use" (domestic language)
- Sponsor name and address
- Storage conditions

- Use-by date
- Number of batch

Two complete sets of study medication will be sent to the study site. The investigator/designee will use the medication set labelled with “study” to be used in the trial. The “reserve” labelled medication set will be used if needed.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and stored according to the labelled storage conditions.

The trial medication must be stored securely, e.g. in a locked cupboard or at a pharmacy. It may only be dispensed to trial subjects according to the protocol by authorised personnel as documented in the form "Investigator's Trial Staff".

All unused or partially used medication must be returned to the sponsor or destroyed after the end of the study. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The Investigator and/or Pharmacist will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol

The Investigator and/or Pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and disposal of unused products at the end of the study.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or at time of destruction, the Investigator/Pharmacist must verify that all unused or partially used drug supplies have been returned/destroyed and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatment and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Primarily, no concomitant therapy will be allowed except for hormonal contraceptives as well as ovary and thyroid hormone replacement. However, in case of adverse events in need of treatment, symptomatic therapy according to the judgment of the investigator will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the electronic case report forms (eCRFs).

In the case of adverse events the subjects will be treated as necessary and if necessary kept under constant supervision at the study site or transferred to hospital until such time that all the results of the evaluations have returned to a medically acceptable level.

4.2.2.2 Restrictions on diet and life style

Subjects should abstain from alcoholic beverages and methyl xanthine containing products for 24 hours, as well as from the intake of any citrus products or apples, for 72 hours prior to each study period and until after the last sample from each period is collected.

While admitted to the trial site the subjects are restricted from consuming any foods or drinks other than those provided by the site staff.

Excessive physical activity (competitive sport etc.) and direct exposure to the sun (including solarium) should be avoided during the whole study.

In each treatment period, the total fluid intake on day 1 should not exceed 2.5 liters.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

4.3 TREATMENT COMPLIANCE

Subjects who are non-compliant, e.g., they do not appear for treatment or violate the restrictions, may be withdrawn from the trial and the eCRF will be completed accordingly (for further procedures).

Compliance will be assured by administration of all study medication under supervision of the investigating physician or a designee at the study site. The measured plasma concentrations will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

The following endpoints will be analysed during the course of the trial.

5.1.1 Primary Endpoint(s)

The following primary endpoints will be determined for the analytes ibuprofen and pseudoephedrine-HCl:

- AUC_{0-tz} (area under the concentration-time curve of the analytes in plasma over the time interval from 0 to the time of last quantifiable time point)
- C_{max} (maximum measured concentration of the analytes in plasma)

5.1.2 Secondary Endpoints

The following secondary endpoints will be determined for the analytes ibuprofen and pseudoephedrine-HCl:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analytes in plasma over the time interval from 0 extrapolated to infinity)

The following secondary endpoints will be determined for the analytes R-ibuprofen and S-ibuprofen:

- AUC_{0-tz} (area under the concentration-time curve of the analytes in plasma over the time interval from 0 to the time of last quantifiable time point)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analytes in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analytes in plasma)
- S/R-ibuprofen ratio for AUC_{0-tz} (i.e., AUC_{0-tz} S-ibuprofen / AUC_{0-tz} R-ibuprofen)

5.2 ASSESSMENT OF EFFICACY

Efficacy measurements will not be performed.

5.3 ASSESSMENT OF SAFETY

Safety and tolerability of the investigational drug(s) will be assessed based on:

- Vital signs (BP, PR)
- 12-lead ECG (electrocardiogram)
- Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
- Adverse events (including clinically relevant findings from the physical examination)
- Assessment of tolerability by the investigator

5.3.1 Physical examination

Physical examination includes assessment of heart, lung, abdomen and measurement of weight and height. Abnormal findings at the time of screening will be recorded as baseline conditions on the appropriate CRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate CRF page.

5.3.2 Vital Signs

Vital signs will be measured after 10 minutes of rest in the supine/sitting position. All recordings shall be made using the same blood pressure recording instrument on the same arm (cf. [Flow Chart](#) for time points). Body temperature will be taken during screening and pre dose.

5.3.3 Safety laboratory parameters

A total amount of ~ 36 mL blood will be taken per subject during the whole course of the study for laboratory parameters. This amount may be exceeded if unscheduled (additional) monitoring of laboratory results is warranted.

The parameters that will be determined are listed in [Table 5.3.3: 1](#) and [Table 5.3.3: 2](#).

The respective reference ranges will be provided in the Investigator Site File (ISF), Section 10 (cf. [Flow Chart](#) for time points of laboratory blood sampling).

The laboratory tests listed in [Table 5.3.3: 1](#) and [Table 5.3.3: 2](#) will be performed at:

PAREXEL Bioanalytical Services Division
Kampuslaan Suid
Campus of the University of the Free State
9301 Bloemfontein
South Africa

The tests listed in [Table 5.3.3: 2](#) constitute exclusionary lab safety tests. These tests may be

repeated as required. Laboratory data will be transmitted to ClinBase™ from where it will be transferred to Data Management electronically.

Pregnancy tests (HCG in urine) will be performed at the trial site (e.g. Expect pregnancy test) on trial days. At screening and at the end of study pregnancy test will be performed in serum.

Table 5.3.3: 1 Routine laboratory tests

Category	Test name
Haematology	Haematocrit (Hct)
	Haemoglobin (Hb)
	Red Blood Cell Count / Erythrocytes
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	White Blood Cells / Leucocytes
	Platelet Count / Thrombocytes
Diff Automatic (relative count)	ESR (only at SCR)
	Neutrophils
	Eosinophils
	Basophils
	Monocytes
	Lymphocytes
Diff Manual (if diff automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils
	Polymorphonuclear (PMN) Eosinophils
	Basophils
	Monocytes
	Lymphocytes
Enzymes	AST/GOT, SGOT
	ALT/GPT, SGPT
	Alkaline Phosphatase (AP/ALP)
	Gamma-Glutamyl Transferase GGT/ γ -GT)
	Lactic Dehydrogenase (LDH)
	Lipase
	Amylase
Substrates	Glucose
	Creatinine
	Bilirubin Total
	Bilirubin Direct
	Bilirubin Indirect
	Protein, Total
	Protein Electrophoresis (only at SCR)
	Albumin
	Alpha-1-Globulin
	Alpha-2-Globulin
	Beta-Globulin
	Gamma-Globulin
	C-Reactive Protein
	Uric Acid
	Urea
Electrolytes	Cholesterol, total Triglycerides
	Calcium Sodium Potassium

Table 5.3.3: 1 Routine laboratory tests cont.

Category	Test name
Hormones	β-HCG (only at SCR and EOS.)
Urine analysis (Stix)	Urin Nitrite
	Urine Protein
	Urine Glucose
	Urine Ketone
	Urobilinogen
	Urine Bilirubin
	Urine Blood
	Urine
	WBC/Leukocytes
	Urine pH
	Urine hCG (trial days)

The following tests will be performed only at screening examination; the results will not be part of the CTR.

Table 5.3.3: 2 Drug Screening and infectious serology

Category	Test name	
Drug screening (Urine)	Cannabis	
	Benzodiazepine	
	Barbiturates	
	Opiates	
	Cocaine	
	Amphetamines	
	Methadone	
	Phencyclidine (phenylcyclohexylpiperidine)	
	Methamphetamine	
	Tricyclic antidepressants	
	Oxycodone	
	Propoxyphene	
	Infectious serology	Hepatitis B Surface Antigen Hepatitis C
		Antibodies
HIV combi (HIV-1 antigen and total antibodies to HIV-1 and HIV-2)		

To encourage compliance, an alcohol breath test may be performed at any time during the study by the discretion of an investigator or designee. The results will not form part of the report.

Baseline laboratory test for substrates, haematology and enzymes will only be performed for safety reasons.

5.3.4 Electrocardiogram

12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using the GE Healthcare CAM14 acquisition module.

The ECGs will be recorded for 10 second duration after the subjects have rested for at least

5 minutes in a supine position. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven. The ECGs will be evaluated by the study investigator or a designate but not imported into the data base, ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant abnormal findings will be reported as adverse events.

ECG-recordings will be made at the time points described in the [Flow Chart](#).

5.3.5 Medical Examination / Global assessment

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and weight, smoking and alcohol history, relevant medical history and concomitant medication, review of inclusion and exclusion criteria, review of vital signs (blood pressure, pulse rate and body temperature), 12-lead ECG, laboratory tests (including a pregnancy test in females), and a physical examination.

The end- of-study examination will include review of vital signs, 12-lead ECG, laboratory tests (including pregnancy test), and a physical examination. Adverse events and concomitant therapies will be assessed throughout the study.

The investigator will assess tolerability based on adverse events and the laboratory evaluation. Tolerability will be assessed by the investigator according to the categories “good”, “satisfactory”, “not satisfactory”, and “bad”.

5.3.6 Assessment of adverse events

The subjects will be required to report spontaneously any AEs as well as the time of onset, duration and intensity of these events. The clinical judgment of the intensity will be made by the physician.

In addition, each subject will be assessed regularly by the medical staff throughout the clinical trial and whenever necessary as deemed by the investigator. Assessment will be made using non-specific questions such as “How do you feel?” Specific questions will be asked wherever required or useful to more precisely describe an AE.

A written record of all AEs shall be kept by the investigator in charge of the study. Records of adverse events shall include data on the time of onset, end time and intensity of the event as well as any treatment or action required for the event and its outcome.

5.3.6.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to 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 product, whether or not considered related to the medicinal product.

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
 - is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
 - requires inpatient hospitalisation or
 - prolongation of existing hospitalisation,
 - results in persistent or significant disability or incapacity, or
 - is a congenital anomaly / birth defect,
- or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as given above.

A copy of the latest list of “Always Serious AEs” will be provided to you upon request. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

No AESIs have been defined for this trial.

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains

unchanged.

5.3.6.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs.

The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards, until individual patient's end of trial:
-all AEs (serious and non-serious).
- After the individual patient's end of trial:
the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs of which the Investigator may become aware of.

The residual effect period (REP) for ibuprofen and pseudoephedrine when measurable drug levels or PD effects are still likely to be present, was defined as 48 hours after administration (based on half-lives of 3 and 8 hours of ibuprofen and pseudoephedrine, respectively). However, for assigning AEs to treatments a conservative approach will be used, i.e. post- treatment periods based on REP will not be defined (see [Section 7.3.3](#)).

AE reporting to sponsor and timelines

The Investigator must report SAEs, and non-serious AEs which are relevant for the reported SAE, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the eCRF and SAE form (if applicable):

- Worsening of pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.
- If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy

In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy an SAE form must be completed in addition.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Date and exact clock time of administration as well as of pharmacokinetic sampling times have to be recorded.

Actual sampling times relative to dosing, rather than nominal times will be used in the calculation of all derived PK parameters.

5.4.2 Methods of sample collection

5.4.2.1 Plasma sampling for pharmacokinetic analysis

PK blood samples will be collected at the following time points:

Table 5.4.2.1: 1 Plasma sampling schedule

Day	Time points of each treatment phase
1	Pre dose , 0:10, 0:20, 0:30, 0:45, 1:00, 1:15, 1:30, 1:45, 2:00, 2:30, 3:00, 4:00, 6:00, 8:00, 10:00, 12:00
2	24:00, 30:00 (total: 19 samples per treatment period)

The actual blood sampling times will be recorded on ClinBase™.

Venous blood samples, 8.5 mL each, for the determination of ibuprofen (including R- and S-ibuprofen) and pseudoephedrine concentrations will be collected into labelled tubes containing dipotassium ethylene-diamine- tetra-acetic acid as anti-coagulant.

Blood samples are routinely placed on ice between sample collection and centrifuging. Within 30 minutes of collection, centrifuging of blood samples will commence at approximately 2700 g within a range of 0°C to 8°C for 10 minutes. Thereafter, the supernatant of each sample will be divided into 4 aliquots (2 aliquots of at least 0.4 mL plasma each for ibuprofen (including R- and S-ibuprofen) analysis, and 2 aliquots of at least 1.3 ml each for the determination of pseudoephedrine) and transferred to labelled, plastic tubes. The plasma samples will be flash-frozen on dry ice immediately after preparation. One of the two aliquots for each analyte will be considered as a duplicate set in case of re-assay.

All sample tube labels will contain at least the following information: study number, analyte, time (protocol time and/or relative sampling time), subject number, blood sample number and treatment period. Plasma samples will be stored at approximately -20°C until transfer to PAREXEL Bioanalytical Services Division (BASD). Pooled samples for concentration range estimation will be prepared according to PAREXEL SOPs. These range estimation samples originate from some of the blood samples collected for drug assays and may be used by the analytical laboratory to determine suitable quantification ranges.

5.4.2.2 Urine sampling for pharmacokinetic analysis

Not applicable

5.4.3 Analytical determinations

Quantitative analysis of ibuprofen (including R- and S-ibuprofen) and pseudoephedrine in the collected plasma samples will be performed by the Bioanalytical Services Division of PAREXEL (BASD) using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

BASD will purchase pure substances of ibuprofen (including R- and S-ibuprofen) and pseudoephedrine from a reputable certified source on behalf of the sponsor. These pure substances will be used as analytical standards for the preparation of calibration standards and quality control samples that will be required for the quantitative analysis of ibuprofen (including R- and S-ibuprofen and pseudoephedrine).

All the samples received at BASD, including samples of subjects who withdrew/were withdrawn, will be analysed. Bioanalytical data will be processed according to the relevant SOPs of BASD.

Complete method validation and bioanalytical reports will be provided.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not applicable.

5.5 ASSESSMENT OF BIOMARKERS(S)

Not applicable

5.6 OTHER ASSESSMENTS

Not applicable

5.7 BLOOD VOLUME

The total blood volume to be collected from each subject during the study is indicated in Table 5.7: 1.

Table 5.7: 1 Total Blood Volume to be collected during the Study

Assay	Volume per sample (mL)	Total number of samples	Total blood volume (mL)
Ibuprofen (including R- and S-ibuprofen) & Pseudoephedrine ¹	8.5	19 x2 treatment periods	323
Haematology	4	4	16
Clinical chemistry ²	5	4	20
Protein Electrophoresis	3.5	1	3.5
Total blood volume (entire study)³			362.5mL

1 Total number of samples and total blood volume are given for both treatment periods.

2 Serum pregnancy tests (females only) at screening and end of study and serology tests at screening will be performed on the sample collected for clinical chemistry. Urine pregnancy tests on admission for period 1 and 2.

3 Excluding repeat laboratory investigations.

5.8 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are appropriate standard measurements and will be performed in order to monitor safety aspects and to determine analyte concentrations for the calculation of pharmacokinetic parameters.

The laboratories of BASD have been certified as Good Laboratory Practice (GLP) compliant, based on the Organization for Economic Cooperation and Development (OECD) guidelines ENV/MC/CHEM (98) 17 revised in 1997. Additionally, the clinical laboratory is accredited according to the International Organization for Standardization / the International Electrotechnical Commission (ISO/IEC) 17025 Standard. Analytical methods are validated according to internationally accepted standards. The quality and integrity of the analytical work generated in this study will be evaluated according to the acceptance criteria, as described in the SOPs of BASD.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. Time windows are permitted as follows:

General medical examination: at screening (1 to 21 days prior to the first study day) and at the end-of-study evaluation (within 7 days following the last trial procedure).

The tolerance for vital signs, ECG and laboratory tests will be provided in a Window Allowance Document.

For planned individual plasma concentration sampling times refer to the [Flow Chart](#). While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

Study measurements and assessments scheduled to occur on study day 1 prior to drug administration have to be performed and completed at least 15 minutes prior to drug administration. This will be addressed in the Window Allowance Document. If a subject misses an appointment, it will be rescheduled if possible.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and the local legislation prior to inclusion to the study.

For the physical and laboratory examinations during the screening visit, cf. [Section 5.3.5](#) and [Section 5.3.3](#).

Drug and virus screening will be performed only at the screening visit.

6.2.2 Treatment period(s)

Each subject will undergo two treatment periods which are separated by a wash-out period between drug administrations. The wash-out period is specified in the [Flow Chart](#). The subjects will be kept under close medical surveillance until discharge from the trial site.

For details on time points for collection of plasma samples for PK analysis, cf. [Flow Chart](#).

For details on time points for all other trial procedures, cf. [Flow Chart](#).

Adverse events and concomitant medication will be evaluated continuously from screening until the end-of-study examination

6.2.3 Follow Up Period and Trial Completion

At the end of the study, the end-of-study evaluation will be performed including a physical examination, measurement of blood pressure and pulse rate, a 12-lead ECG, standard laboratory tests, and pregnancy testing.

All clinically significant abnormal values (including laboratory parameters) will be followed up using the appropriate tests until a return to a medically acceptable level is achieved.

Adverse events persisting after trial completion must be followed up, until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned. A SAP will be prepared with more details on the planned statistical methodology and will be finalized prior to database lock.

If applicable, deviations from the original SAP and reasons for the deviations, as well as any alternative or additional statistical analysis that may be performed, will be documented in the CTR.

The objective of the trial is to establish the bioequivalence of **Test treatment (T)**, one fixed dose combination tablet compared to reference treatment (R) **RhinAdvil®** two fixed dose combination tablets given to healthy male and female subjects.

The study will be conducted according to an open-label, randomised, single-dose, two-way crossover design. For bioequivalence studies, the crossover design is viewed favourably due to its efficiency: since each subject serves as his/her own control, the comparison between formulations is based on a comparison within subjects rather than between subjects. This means that the inter-subject variability is removed from the comparison between formulations ([R94-1529](#)).

Bioequivalence is primarily to be determined on the basis of the endpoints AUC_{0-tz} and C_{max} of the analytes, ibuprofen and pseudoephedrine-HCL. Additionally, $AUC_{0-\infty}$ and other secondary endpoints that are described in [Section 5.1.2](#) will be calculated undergoing the same analyses as described for the primary endpoints (estimation of relative bioavailability). The derivation of the PK parameters will be specified in the TSAP.

Safety and tolerability will be determined on the basis of the following parameters: adverse events, laboratory tests, physical examination, vital signs (BP, PR), 12-lead ECG, and assessment of tolerability by the investigator.

The statistical model used for the analysis of the AUC_{0-tz} , C_{max} and $AUC_{0-\infty}$ will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and 'treatment'. All effects will be considered as fixed. The model is described by the following equation

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}, \text{ where}$$

y_{ijkm} = logarithm of response (AUC or C_{max}) measured on subject m in sequence i receiving treatment k in period j ,

μ = the overall mean, ζ_i = the i th sequence effect, $i = 1, 2$,

s_{im} = the effect associated with the m th subject in the i th sequence, $m = 1, 2, \dots, 24$

π_j = the j th period effect, $j = 1, 2,$

τ_k = the k th treatment effect, $k = 1, 2,$

e_{ijkm} = the random error associated with the m th subject in sequence i who received treatment k in period j .

7.2 NULL AND ALTERNATIVE HYPOTHESES

Bioequivalence is established by using the average bioequivalence method to ensure that the ratio of the primary endpoints of the two treatments (T/R) is contained within a pre-specified acceptance range (see below). This goal is accomplished by testing the below hypothesis on the log scale.

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta$ or $\mu_T - \mu_R \geq \delta$

(i.e. the difference of the population average responses is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range),

Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$

(i.e. the difference of the population average responses is both greater than the lower bound and less than the upper bound of the acceptance range), where μ_T and μ_R are the population average responses of the log-transformed measures for the formulations Test and Reference, and δ is the bioequivalence limit that defines the acceptance range for AUC and C_{max} on the logarithmic scale

In this trial, δ is taken to be $\ln(1.25)$. This translates to an acceptance range of 80 to 125% for the geometric mean of the ratio of the parameters on the original scale.

This hypothesis and its alternative can be decomposed into two one-sided null hypotheses, H_{01} and H_{02} , with their accompanying alternatives:

H_{01} : $\mu_T - \mu_R \leq -\delta$ vs. H_{a1} : $\mu_T - \mu_R > -\delta$

H_{02} : $\mu_T - \mu_R \geq \delta$ vs. H_{a2} : $\mu_T - \mu_R < \delta$

Due to the nature of normal-theory confidence intervals, the test of the null hypothesis at the $\alpha = 0.05$ level is equivalent to carrying out two one-sided tests of the above null hypotheses each at the $\alpha = 0.05$ level of significance. The rejection of both null hypotheses H_{01} and H_{02} at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The PK analysis population (PKS, PK set) will include all treated subjects that provide observations for both periods for at least one primary endpoint evaluable (see below) and without any major protocol deviation thought to interfere with the absorption, distribution, metabolism, and excretion of the compound to be measured. PK parameters for subjects who discontinue after a single treatment may be presented in the listings but will not be used for summary statistics or any statistical analysis.

The total ibuprofen and pseudoephedrine pharmacokinetic parameters AUC_{0-tz} and C_{max} of test (T) and reference will be log transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for $\log(T)-\log(R)$ will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

A claim of bioequivalence will be made if the 90% confidence intervals of the geometric means of both ratios AUC_{0-tz} and C_{max} of ibuprofen and pseudoephedrine-HCL are contained in the pre-defined acceptance range.

7.3.2 Secondary analyses

The parameter $AUC_{0-\infty}$ of total ibuprofen and pseudoephedrine will statistically be assessed using the same methods as described for the primary endpoints.

Additionally, R- and S-ibuprofen pharmacokinetic parameters AUC_{0-tz} , $AUC_{0-\infty}$ and C_{max} will statistically be assessed using the same methods as described for the primary endpoints (analysis of relative bioavailability). The same methods will be applied for the S/R-ibuprofen ratio for AUC_{0-tz} .

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report.

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the geometric mean and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for plasma concentrations as well as for all primary and secondary pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, geometric coefficient of variation. The data format for descriptive statistics of concentrations will be defined in the TSAP.

7.3.3 Safety analyses

All subjects who received at least one dose of study drug will be included in the safety evaluation (safety population). Safety analyses will be descriptive in nature and will be based on BI standards

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see [Section 4.1](#)) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). In general, all adverse events occurring between start of treatment and end of the residual effect period are considered 'treatment-emergent'. The residual effect period (REP) was defined as 2 days which is shorter than the wash-out period. In the special setting of single doses in the cross-over design AEs will be assigned to treatments as detailed below without taking into account the residual effect period separately.

AEs will be assigned to treatments based on start date/time of the AE in relation to dosing in each period.

- All AEs with start date/time prior to dosing in period 1 are pre-treatment AEs and will be assigned to screening.
- All AEs with start date/time after the date/time of dosing in period 1, but before dosing in period 2, will be assigned to the treatment received in period 1.
- AEs with start date/time after the date/time of dosing in period 2 will be assigned to the treatment received in period 2.

With this definition AEs occurring in wash-out will be assigned to the treatment received in period 1. AEs up to the follow-up visit will be assigned to the treatment received in period 2 if the start date/time of the AE was after dosing in period 2.

Independent of this rule, the relationship of an adverse event to the treatments will be assessed by the investigator.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, and other significant AEs (according to ICH E3) will be listed separately.

Global tolerability will be assessed by the Investigator.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.5.2 Plasma concentration – time profiles

Concentration data identified with NS (no sample), NR (not reportable) and BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NR and NS are included).

7.5.3 Pharmacokinetic parameters

In the non-compartmental analysis, concentration data identified with NS and NR will not be considered. BLQ in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

Data may/will be excluded from PK analysis (concentrations listed only) if any of the following criteria are fulfilled:

- The pre-dose concentration is greater than 5% of the corresponding C_{\max} in any given treatment period.
- Subject experienced emesis within 2 x the reported median t_{\max} for the analyte (Median t_{\max} is to be determined excluding the subjects experiencing emesis).

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

Subjects will be randomised to one of the two treatment sequences (T-R, R-T) in a 1:1 ratio. Stratification by gender will not be done.

The randomisation schedule will be provided by PAREXEL Biostatistics. The randomisation schedule will be generated utilizing the PROC PLAN procedure of SAS® software.

7.7 DETERMINATION OF SAMPLE SIZE

The intra-individual variability of the primary endpoints of both analytes was determined based on a similar internal study (1024.7) with the same test and reference products but lower doses. For C_{\max} the coefficient of variation (gCV) was estimated below 19 % for both analytes, while for AUC, the gCV for both analytes was lower than 12%. For C_{\max} the T/R ratio estimate (gMean) was not lower than 91%, for AUC not greater than 105%.

Hence the sample size for this trial was determined based on the C_{max} , accounting for multiple testing of the two analytes, i.e. the overall power of the study is the product of the power of the test of each analyte, as their endpoints are assumed to be uncorrelated. Using gCVs of 19 and 20% and a power of 95% for the single test (in order to achieve an overall power greater than 90%) to reject the null hypothesis of bio-inequivalence for C_{max} in favour of equivalence at the 5% level of significance is displayed in Table 7.7: 1 under various assumptions for the T/R-subject ratio. The total sample size is double the size per sequence group.

Table 7.7: 1 Required sample sizes per sequence to achieve an overall power greater than 90% for concluding equivalence (with respect to an acceptance range of 80-125%) assuming a coefficient of variation of 19% or 20% and various intra-subject ratios, for a two-way crossover based on C_{max} data of 1024.7 (ibuprofen)

gCV	20	20	19	20	20	20
T/R Ratio¹	90%	91%	91%	92%	100%	105%
Power of Single Test	95%	95%	95%	95%	95%	95%
Overall power	91%	91%	91%	91%	91%	91%
N per sequence group	32	27	24	23	11	15

¹ This ratio reflects the median intra-subject ratio defined by $\exp(\mu_T)/\exp(\mu_R)$ and is estimated by the geometric mean of the intra-subject ratios

From the above table, a sample size of 48 will have a more than 90% power to conclude bioequivalence if the T/R ratio is not lower than 91%, the lowest ratio in study 1014.7 (C_{max} of ibuprofen). Accounting for up to 8 dropouts, a total of $N = 48 + 8 = 56$ subjects will be entered into the study

The calculation was performed as described by Diletti et al (cf. [R94-1445](#)) using nQuery.

The calculation was performed using the MTE2co routine from commercial software nQuery Advisor[®] [[R07-0364](#)].

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant PXL and BI Standard Operating Procedures (SOPs), and other relevant regulations.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP*.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report. The certificate of insurance cover is made available to the Investigator and the subjects, and is stored in the ISF (Investigator Site File).

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to subject participation in the trial, written informed consent must be obtained from each subject according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

8.2 DATA QUALITY ASSURANCE AND DATA MANAGEMENT

8.2.1 Data Quality Assurance

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.2.2 Data Management

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11

requirements. A data management plan (DMP) will be prepared to describe the work- and data-flow within the clinical study. If applicable, sponsor-specific requests, timelines, versions for the computer systems and the coding will be defined in the DMP. The DMP must be finalized before data entry. Different levels of data validation checks may be developed based on the different data sources. A data validation specification (DVS) may be created if not covered by standard processes. In such case study-specific checks will be added to the standard checks that are already available. If applicable the DVS must be finalized before data validation. The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the investigator for answers. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). This process will be repeated until no further discrepancies are found. The study monitor will confirm that all queries have been closed out appropriately. The data will be then be declared as clean. Applicable documentation will be stored in the study files. Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

8.3 RECORDS

For drug accountability, refer to [Section 4.1.8](#).

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in [Section 8.3.1](#). The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject privacy will be ensured by using study subject number.

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Storage of biological samples

The principal investigator or designee will ensure that all biological fluids collected during the study will not be used for purposes other than as directed by the clinical study protocol. All collected biological fluids used for safety investigations will be destroyed within 3 months after the clinical execution of the study has been completed.

Unused duplicate plasma PK samples will be stored at BASD for up to 6 months after completion of the bioanalysis phase of the study. The Sponsor will be required to indicate whether additional storage is needed or whether the samples may be discarded.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial. The **end of the trial** is defined as the date of the last visit of the last subject in the trial ("Last Patient Out") **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all subjects have completed the trial.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

9. REFERENCES

9.1 PUBLISHED REFERENCES

- P88-35100 Sperber SJ, Hayden FG. Chemotherapy of Rhinovirus Colds. Antimicrob Agents Chemother 1988;32:409-419.
- P97-6591 Michel FB. Multisymptom management in the common cold. Int Pharm J 1996;10(5)(Suppl):4-9.
- P04-01312 Moore N, Parc JM le, Ganse E van, Wall R, Schneid H, Cairns R. Tolerability of ibuprofen, aspirin and paracetamol for the treatment of cold and flu symptoms and sore throat pain. Int J Clin Pract 2002; 56(10):732-734.
- R94-1445 Diletti E, Hauschke D, Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. Int J Clin Pharmacol Ther Toxicol 1992;30(Suppl 1):S51-S58.
- R94-1529 Chow SC, Liu JP, editors. Design and Analysis of Bioavailability and Bioequivalence Studies. New York: Marcel Dekker Inc; 1992.
- R07-2230 Taverner D, Latte J. Nasal decongestants for the common cold (review). Cochrane Database Syst Rev 2007(1).
- R07-0364 Elashoff JD. nQuery Advisor version 6.0 user's guide. Cork: Statistical Solutions 2005
- R09-2316 Luecker PW, Birkel M, Hey B, Loose I, Schaefer A. Relative bioavailability and bioequivalence of a newly developed fixed combination sachet of acetylsalicylic acid and pseudoephedrine compared with a preliminary combination. Methods Find Exp Clin Pharmacol 2003;25(8):631-637.
- P10-06083 Sperber SJ, Sorrentino JV, Riker DK, Hayden FG. Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds. Symp on Combination Therapies: New and Emerging Uses for Cyclooxygenase Inhibitors, Calcium Blockers, and Biological Response Modifiers on Immunity, New York, 2 - 3 Jun 1988. Bull NY Acad Med 1989;65(1):145-160.
- R13-2920 ArrudaE, Pitkaranta A, Witek TJ, Doyle CA, Hayden FG Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 35 (11), 2864 - 2868 (1997)

9.2 UNPUBLISHED REFERENCES

Not applicable

10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the revised protocol according to Amendment 01

Number of global amendment	01
Date of CTP revision	20 February 2017
EudraCT number	Not applicable
BI Trial number	1024.9
BI Investigational Product(s)	Fixed dose combination 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl film-coated tablet
Title of protocol	Bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl compared to two film-coated fixed dose combination tablets RhinAdvil® (200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) administered in at least 48 healthy male and female subjects (Open-label, randomised, laboratory blind, single dose, two-way crossover, Phase I trial).
To be implemented only after approval of the IRB / IEC / Competent Authorities	Yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	No
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	No
Section to be changed	See tracked version of the amended protocol for the sections where changes were made.

Description of change	<p>Addition of a secondary trial objective to assess the bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl vs. RhinAdvil® (2 tablets containing 200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) as a fixed dose combination tablet with respect to R- and S-ibuprofen (enantiomers of ibuprofen).</p> <p>Updating applicable sections of the trial protocol to provide for the added PK analyses of R- and S-ibuprofen.</p> <p>Due to technical problems, document number extension needs to be -03 and due to second-step signature workflow needed, document number extension -04 is current.</p>
Rationale for change	To add an additional secondary trial objective.

APPROVAL / SIGNATURE PAGE**Document Number: c11001605****Technical Version Number:4.0****Document Name: clinical-trial-protocol-version-03**

Title: Bioequivalence of a fixed dose combination tablet containing 400 mg Ibuprofen and 60 mg Pseudoephedrine-HCl compared to two film coated fixed dose combination tablets RhinAdvil® (200 mg Ibuprofen and 30 mg Pseudoephedrine-HCl) administered in at least 48 healthy male and female subjects (Open-label, randomized, laboratory blind, single dose, two-way crossover, Phase I trial).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Monitor	██████████	24 Feb 2017 10:57 CET
Author-Trial Statistician	██████████	24 Feb 2017 10:57 CET
Approval-Therapeutic Area █████	██████████	24 Feb 2017 12:45 CET
Approval-Team Member Medicine	██████████	24 Feb 2017 15:29 CET
Verification-Paper Signature Completion	██████████	24 Feb 2017 15:32 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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