TITLE PAGE

Clinical Study Protocol

A SINGLE CENTER, MULTIPLE-DOSE, OPEN-LABEL, RANDOMIZED, THREE-PERIOD CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF DICLOFENAC IN THE TOPICAL GEL COMBINATION PRODUCT (DICLOFENAC 2% + CAPSAICIN 0.075%) COMPARED TO DICLOFENAC MONO GEL 2% AND VOLTAROL® 12 HOUR EMULGEL 2.32% GEL IN AT LEAST 42 HEALTHY MALES AND FEMALES

[redacted] **STUDY NUMBER:**	[redacted]229554
SPONSOR STUDY NUMBER:	1358.2
DOCUMENT NUMBER:	c09839764-02
TEST PRODUCTS:	Diclofenac Mono Gel 2% (Test 1) Combination of Diclofenac 2% + Capsaicin 0.075% Topical Gel (Test 2)
REFERENCE PRODUCT:	Voltarol® Emulgel 2.32%
DEVELOPMENT PHASE:	Phase I Relative Bioavailability Study
SPONSOR:	Boehringer Ingelheim Pharma GmbH & Co. KG
STUDY CENTER:	[redacted]
REGION OF SUBMISSION:	Europe
ORIGINAL PROTOCOL:	Final 1.0, 17 October 2016
REVISED PROTOCOL ACCORDING TO AMENDMENT NO. 1:	Final 1.0, 13 February 2017

Document prepared in Microsoft Word® 2010.

SYNOPSIS

Title of the Study

A SINGLE CENTER, MULTIPLE-DOSE, OPEN-LABEL, RANDOMIZED, THREE-PERIOD CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF DICLOFENAC IN THE TOPICAL GEL COMBINATION PRODUCT (DICLOFENAC 2% + CAPSAICIN 0.075%) COMPARED TO DICLOFENAC MONO GEL 2% AND VOLTAROL® 12 HOUR EMULGEL 2.32% GEL IN AT LEAST 42 HEALTHY MALES AND FEMALES

Study Objectives

The main objective of this study is to assess the relative systemic bioavailability of diclofenac in the presence and absence of capsaicin by comparing the systemic bioavailability of diclofenac from a combination product (Diclofenac 2% + Capsaicin 0.075% Topical Gel) with two diclofenac only products, Diclofenac Mono Gel 2% and Voltarol® 12 Hour Emulgel 2.32% Gel, following topical administration. [redacted]

In order to examine potential racial differences in pharmacokinetics (PK), the study population will be stratified 50:50, Caucasian versus Black people. With respect to the main objective, additionally a supportive analysis will be performed to investigate the influence of race on the intra-individual bioavailability ratios.

Study Design

The study will comprise:

- Screening period of maximum 21 days;
- Three-treatment periods (each of which will include a multiple dose period of 7 days [twice daily and only in the morning on Day 7] and two PK profile periods of 12 hours [Day 1] and 24 hours [Day 7]) separated by a wash-out period of at least 7 calendar days between the last administration of the investigational medicinal product (IMP) in a treatment period and the first administration of IMP in the next treatment period. Clinic stay/visits will be as follows:
  - Subjects will be admitted to the study center on Day -1 and leave the center after the morning dose on Day 2 at least 24 hours after the initial dosing on Day 1
  - Subjects will visit the study center on Days 3 and 4 for the morning dose
  - On Day 5, they will visit the center for PK blood sampling prior to morning and evening doses and will be re-admitted to the study center on the evening of Day 5
  - Subjects will leave the center at least 24 hours after the morning dose on Day 7
- A follow-up visit will occur within 72 hours after completion of the last treatment period of the study.

Before the first administration of IMPs subjects will be randomized to one of 6 treatment sequences stratified by race (Black, Caucasian), i.e., 4 Black and 4 Caucasian subjects will be assigned to each treatment sequence.

The duration of this study is expected to be approximately 38 days per subject (excluding the screening period).

Clinic Stay

Subjects will be admitted to the study center on Day -1 and on the evening of Day 5 and are allowed to leave at least 24 hours after first dosing on Day 1 and at least 24 hours after the morning dose on Day 7.

Pharmacokinetic Sampling Times

For the determination of diclofenac and diclofenac + capsaicin PK, blood samples will be collected on Day 1 at the following time points: 0 hours (prior to morning dose) and at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose (prior to evening dose) (total: 10 samples per treatment period) and on Day 7 pre-dose at 0 hours and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours post-dose (15 samples per treatment period). Additional blood samples to establish attainment of steady state will be collected on Days 5 and 6 (prior to morning dose and evening dose).

Blood Volume

The total blood volume to be collected from each subject during the study should not exceed 308 mL (repeat laboratory investigations not included).

Study Population

The study population for this study will be stratified 50:50 (Caucasians versus Black People) and subjects who meet the inclusion criteria will be considered eligible to participate in the study.

Inclusion Criteria:

1. Healthy males and females, 18 to 50 years (inclusive) at time of screening.
2. Body mass index between 18.5 and 29.9 kg/m^2 (inclusive).
3. Body mass not less than 50 kg for males and females.
4. Findings for medical history, vital signs, physical examination, standard 12-lead electrocardiogram (ECG) and laboratory investigations must be normal or within laboratory reference ranges for the relevant laboratory tests, unless the Principal Investigator (PI) considers the deviation to be not clinically significant for the purpose of the study.
5. Non-smokers.
6. Females, if:
   - Not of childbearing potential, e.g., has been surgically sterilized, undergone a hysterectomy, amenorrhea for ≥ 12 months and considered post-menopausal,

     Note: In post-menopausal women, the value of the serum pregnancy test may be slightly increased. This test will be repeated to confirm the results. If there is no increase indicative of pregnancy, the female will be included in the study.
   - Of childbearing potential, the following conditions are to be met:
     - Negative pregnancy test
     - If this test is positive, the subject will be excluded from the study. In the rare circumstance that a pregnancy is discovered after the subject received the IMP; every attempt must be made to follow her to term
     - Not lactating
     - Abstaining from sexual activity (if this is the usual lifestyle of the subject) or must agree to use an accepted method of contraception, and agree to continue with the same method throughout the study
     - In this study the concomitant use of hormonal contraceptives is allowed
     - Examples of reliable methods of contraception include oral (documented that the dose has been stable for at least one month before the first intake of the IMP), injectable or implantable contraceptives, non-hormonal/hormonal intrauterine device, and barrier methods combined with an additional contraceptive method
     - Other methods, if considered by the PI as reliable, will be accepted
7. Written informed consent given for participation in the study.

Investigational Medicinal Products

Test Product 1(A)

Generic name	:	Diclofenac sodium
Trade name	:	Diclofenac mono gel 2%
Dosage form	:	Immediate release topical gel
Dose	:	Multiple doses (2 g, bid) of Diclofenac 2%
Route of administration	:	Topical
Manufacturer	:	Boehringer Ingelheim Pharma GmbH & Co. KG
Country of origin	:	Germany

Test Product 2 (B)

Generic name	:	Diclofenac + Capsaicin

Product name	:	Combination of Diclofenac 2% + Capsaicin 0.075% formulation
Dosage form	:	Immediate release topical gel
Dose	:	Multiple doses (2 g, bid) of Diclofenac 2% + Capsaicin 0.075%
Route of administration	:	Topical
Manufacturer		Boehringer Ingelheim Pharma GmbH & Co. KG
Country of origin	:	Germany
Reference Product (C)		
Generic name	:	Diclofenac sodium topical gel
Trade name	:	Voltarol® 12 Hour Emulgel 2.32% Gel
Dosage form	:	Immediate release topical gel
Dose	:	Multiple doses (2 g, bid) of Voltarol (Diclofenac sodium 2.32%)
Route of administration	:	Topical
Manufacturer	:	Novartis Consumer Health UK Ltd.
Country of origin	:	United Kingdom

Analytes
Diclofenac and capsaicin

Sample Size
Up to 48 eligible subjects (stratified 50:50 Caucasian versus Black people) will be enrolled into the study, to complete the study with at least 42 evaluable subjects.

Pharmacokinetic Endpoints
Primary and secondary endpoints are only calculated for diclofenac.

Primary Pharmacokinetic Endpoints:

- Area under the plasma concentration-time curve (AUC) over one dosing interval (τ = 12 hours) ($AUC_{0-\tau,ss}$) (Day 7)
- Maximum plasma drug concentration during a dosage interval ($C_{max,ss}$) obtained directly from the concentration-time data (Day 7)

Secondary Pharmacokinetic Endpoints:

- Time to maximum observed plasma concentration at steady state ($t_{max,ss}$) (Day 7)
- Average plasma concentration ($C_{av,ss}$) calculated as $AUC_{0-\tau,ss}/\tau$, τ is one dosing interval (12 hours)
- Percentage peak-trough fluctuation (%PTF), calculated as $[100*(C_{max,ss} - C_{pre,ss})/C_{av,ss}]$

[redacted]

Safety Variables (other endpoints)

Safety variables will include vital signs, 12-lead ECG, hematology, clinical chemistry, pregnancy test results, overall assessment of tolerability [redacted] Adverse events (AEs) and concomitant medication will also be reported.

Statistical Analysis

Pharmacokinetic population:

The PK population will consist of all subjects in the safety population for whom at least one of $AUC_{0-\tau,ss}$ or $C_{max,ss}$ can be calculated for one treatment and who have no major protocol deviations thought to impact on the analysis of the PK data.

Relative bioavailability will be estimated for diclofenac by the ratios of the geometric means for the steady-state $AUC_{0-\tau}$ and $C_{max,ss}$. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including fixed effects for sequence, subject nested within sequence, period and treatment. For each endpoint, the difference between the expected means for log(Test)-log(Reference) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). CIs will be calculated based on the residual error from ANOVA. The differences between the test and reference product and the CIs will be back-transformed to the original scale, resulting in point estimates of the Test/Reference gMean ratios and 90% CIs.

The following comparisons will apply:

- Test Product 2 vs Reference
- Test Product 2 vs Test Product 1

Only the data for the comparison under investigation will be included in the statistical analysis i.e., when comparing Test Product 2 and Reference, the data for the Test Product 1 will be removed from the dataset. Only subjects with observations for both treatments will be included in each comparison. [redacted]

The effect of race on relative bioavailability will be analyzed separately as supportive analysis,, supportive because race is not expected to influence intra-individual bioavailability ratios. The statistical model of the supportive analysis will be an ANOVA on the logarithmic scale including fixed effects for sequence, period, race, treatment, treatment and race interaction and subject nested within sequence and race interaction. The effect of race will be checked and for each endpoint, least squares means by treatment and race will be tabulated. Point estimates of the T/R gMean ratios and 90% CIs will be presented by race in the same way as for the main analysis.

Capsaicin concentrations will be analyzed descriptively.

Safety population:

All subjects who received at least one dose of IMP will be included in the safety analysis of the study.

Safety data will be listed as applicable.

Hematology and clinical chemistry values will be listed and summarized. Abnormal hematology and clinical chemistry values will be flagged in the listings.

Electrocardiograms will be classified as “Normal”, “Abnormal not clinically significant”, “Abnormal clinically significant”, and listed and summarized. Vital signs will be flagged for measurements that are outside the reference range and listed, including changes from baseline. Summary statistics will be provided.

Prior and concomitant medication will be coded and listed separately.

[redacted] and data from inspection of IMP application site will be listed. Overall assessment of

tolerability will be listed.

Additional listings will be presented for physical examination, urinalysis, pregnancy testing, serology and drugs of abuse and tobacco use.

SIGNATURE: SPONSOR SIGNATORY

A SINGLE CENTER, MULTIPLE DOSE, OPEN-LABEL, RANDOMIZED, THREE-PERIOD CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF DICLOFENAC IN THE TOPICAL GEL COMBINATION PRODUCT (DICLOFENAC 2% + CAPSAICIN 0.075%) COMPARED TO DICLOFENAC MONO GEL 2% AND VOLTAROL® 12 HOUR EMULGEL 2.32% GEL IN AT LEAST 42 HEALTHY MALES AND FEMALES

[redacted]STUDY NUMBER: PXL229554

SPONSOR STUDY NUMBER: 1358.2

I hereby declare that I have reviewed this clinical study protocol and that I approve its contents

[redacted]

Signature

14 Feb 2017

Date of Signature

[redacted]

Senior Medical Advisor

Boehringer Ingelheim Pharma GmbH & Co. KG

STATEMENT AND SIGNATURE: PRINCIPAL INVESTIGATOR

A SINGLE CENTER, MULTIPLE-DOSE, OPEN-LABEL, RANDOMIZED, THREE-PERIOD CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF DICLOFENAC IN THE TOPICAL GEL COMBINATION PRODUCT (DICLOFENAC 2% + CAPSAICIN 0.075%) COMPARED TO DICLOFENAC MONO GEL 2% AND VOLTAROL® 12 HOUR EMULGEL 2.32% GEL IN AT LEAST 42 HEALTHY MALES AND FEMALES

[redacted] STUDY NUMBER: [redacted]229554

SPONSOR STUDY NUMBER: 1358.2

I, the undersigned, verify that, to the best of my abilities and knowledge:

1. I have reviewed this clinical study protocol and approve its contents.
2. I am familiar with the properties of the investigational medicinal product as described in the References. I am qualified by scientific training and experience to conduct the clinical investigational study identified above. My medical education and experience is stated in the curriculum vitae provided.
3. The study center has adequate study staff and appropriate facilities (including laboratories) that will be available for the duration of the study to be conducted in conformance with this clinical study protocol and Good Clinical Practices ([GCP] including the South African Clinical Trials guidelines), as assured by an in-house quality assurance program.
4. I agree to obtain permission from the Sponsor in writing should any changes be required to the clinical study protocol. Should the safety of the subjects necessitate immediate action, which represents a deviation from the clinical study protocol, the Sponsor will be informed as soon as possible.
5. I shall obtain in writing the necessary approval from the independent ethics committee (IEC) and the Medicines Control Council (MCC). I shall ensure communication of any modification, amendment or deviation of the clinical study protocol, and also

inform the IEC and the MCC in the event of discontinuation of the study and the reasons for discontinuation.

6. I agree to obtain written informed consent from all potential subjects before performance of any study-related activity. Subject study information will be provided in the language the potential subject prefers.

7. I shall ensure that case report forms are completed, signed and archived at the study center as applicable.

8. I agree to allow the auditor/inspector/any representatives of regulatory authorities access to all relevant documents and be available to discuss any findings/issues.

9. I shall ensure that the confidentiality of all information about subjects is respected by all persons involved, as well as information supplied by the Sponsor. Any disclosure of such information will only be made subject to the Sponsor's written approval.

10. I agree to render a clinical study report of my findings at the end of this study, suitable for regulatory purposes, whether or not the study has been completed.

11. In my absence one of the co-investigators, approved for participation in this study, will act as Principal Investigator (PI) for study-related decisions.

[redacted]

Signature

14 FEB 2017

Date of Signature

[redacted]

Name (in print):

Academic Qualification(s):

Job Title:

Address of Study Center:

Telephone Number:

Fax Number:

Email Address:

1. TABLE OF CONTENTS

1.1. List of Tables

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

%PTF	Percentage peak-trough fluctuation
β-HCG	Beta human chorionic gonadotropin
Adverse event reporting	Adverse events will be documented from the time that the informed consent document (ICD) has been signed
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
[redacted]	[redacted]
[redacted]	[redacted]
$AUC_{(0-\tau,ss)}$	Area under the plasma concentration-time curve over one dosing interval (τ= 12 hours) at steady state
BASD	[redacted] Bioanalytical Services Division
BI	Boehringer Ingelheim Pharma GmbH & Co. KG
BLQ	Below the limit of quantification
BMI	Body mass index
$C_{av,ss}$	Average plasma concentration at steady state
CI	Confidence interval
Citrus fruits	Any of numerous fruits of the genus *Citrus* e.g., orange, lemon, lime, grapefruit and tangerine
Clinic day	Time ranging from the start of the profile period until discharge from the clinic
[redacted]	[redacted]
$C_{max,ss}$	Maximum steady-state plasma drug concentration during a dosage interval
Completer	Enrolled subject who completes the entire study
Concomitant medication	Any medication given in addition to the IMP
CRF	Case report form
CS	Clinically significant (abnormalities)
CSR	Clinical Study Report
CV	Coefficient of variation

C_{pre}	Observed plasma concentration at the end of a dosing interval, immediately preceding the next dose
[redacted]	[redacted]
DCF	Data clarification form
DEDP	Drug exposure during pregnancy
DILI	Drug-induced liver injury
DMP	Data management plan
DRM	Data review meeting
[redacted]	[redacted]
DVS	Data validation specification
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency (established 1995)
Enrolled subject	Person allocated a subject number which confirms formal entry into the study
EU	European Union/European Community
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GGT	Gamma glutamyl transferase (transpeptidase)
GLP	Good Laboratory Practice
gMean	Geometric mean
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
ISF	Investigator site file
K_2-EDTA	Potassium-ethylenediaminetetraacetic
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MCC	Medicines Control Council (of South Africa)
Medication number	Number of tube with medication used to track the tubes
n	Number of subjects

NCS	Not clinically significant (abnormalities)
NOA	Not analyzed
Non-smoker	Subject who has not smoked previously and/or has not used nicotine or nicotine-containing products for at least 3 months; subjects who have discontinued smoking or the use of nicotine/nicotine-containing products (including snuff and similar products) at least 3 months before the first administration of the IMP
NOR	No valid result
NSAID	Nonsteroidal anti-inflammatory drug
NSAID	Non-steroidal anti-inflammatory drug
[redacted]	[redacted]
PI	Principal Investigator
PK	Pharmacokinetic(s)
Profile period	Pharmacokinetic blood sampling period, including clinic stay
REP	Residual effect period
Replacement	Eligible subject who enters the study to replace a subject who withdrew or was withdrawn from the study
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Screening period	Time window during which potential subjects are evaluated to establish eligibility for enrollment into the study
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
Standby	A subject (screened within the required time period before the first administration of the IMP, considered eligible but not enrolled as the required number of subjects for enrollment has been met) available as a replacement
Study start	Study start is defined as administering or giving directions for the administration of the IMP to a subject for the purposes of this study
[redacted]	[redacted]
$t_{max,ss}$	Time to maximum observed plasma concentration at steady state
Treatment period	Time between the first and last study-related procedures of a period of IMP administration
TRPV1	Transient receptor potential vanilloid 1

ULN	Upper limit of normal
Wash-out period	Period between consecutive administrations of IMP
Withdrawal	Enrolled subject who is withdrawn by the Investigator before the clinical phase of the study has been completed
[redacted]	[redacted]

3. ETHICS

3.1. Mandatory Approvals and Protocol Amendments

Written approval for the final version of the clinical study protocol and any amendments (if applicable), as well as other applicable documents will be obtained from an IEC and the MCC of South Africa before performance of any study-related procedures.

Independent Ethics Committee

Ethics Committee of the Faculty of Health Sciences
Research Division
Internal Post Box G40
Campus of the University of the Free State
9301 Bloemfontein
South Africa
Tel: +27 51 405 2812
Fax: +27 51 444 4359

This protocol is to be followed exactly. Amendments must be written to alter the protocol. However, in the event of any medical emergency, the PI is free to institute any medical procedure he/she deems appropriate. Such events and procedures must be reported promptly to the Sponsor (Boehringer Ingelheim Pharma GmbH & Co. KG).

Amendments will be made available to study protocol recipients.

3.2. Ethical Conduct of the Study

The study will be conducted in compliance with this clinical study protocol and ethical principles that have their origins in the Declaration of Helsinki, including the following guidelines:

- Department of Health, South Africa (Guidelines for Good Practice, 2006)
- International Council for Harmonisation (ICH) Guideline for GCP (2002) which meets the ethical requirements of the European Union (EU) Clinical Trials Directive 2001/20/EC, 04 April 2001 and Directive 2005/28/EC, 08 April 2005

3.3. Subject Information and Informed Consent

Before commencement of the screening procedures, the potential subjects will be informed verbally by the Investigator and in writing by way of the informed consent document (ICD) concerning the nature, purpose and risks involved in the screening procedures, as well as the procedures, restrictions, obligations, remuneration, insurance coverage and possible adverse drug reactions relevant to the study.

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the potential subjects in non-technical terms. Potential subjects will be required to read, sign and date the ICD before enrollment. They will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each potential subject will be given a signed copy of the ICD.

The original, as well as any revision of the ICD provided to the subjects, will be submitted for ethics approval.

Representative written information for the subjects and sample consent forms will be kept in the investigator site file (ISF).

3.3.1. Confidentiality

Study data will be stored in accordance with local and global data protection laws. Information on confidentiality is also contained in the ICD.

Potential subjects will be informed that representatives of the Sponsor, IEC, regulatory authorities or auditors may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. All communications and documents relevant to subjects in the study will identify each person only by the subject's study number.

3.3.2. Remuneration of Subjects

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how subjects will be compensated is contained in the ICD.

3.3.3. Indemnity

Insurance coverage has been arranged to indemnify the subjects in the event of death or any deterioration in health or well-being caused by participation in the study.

The certificate of insurance will be kept in the ISF.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator and Study Staff

Information on the Investigators and other persons whose participation will materially affect the conduct of the study is contained in the ISF.

Study Center

[redacted] ♣

Physical address: [redacted]

Postal address: [redacted]

Tel: [redacted] (Reception)

Fax: [redacted]

Routine Safety and Analytical Laboratory

[redacted]

Physical address: [redacted]

Postal address: [redacted]

Tel:

Fax: [redacted]

Statistical Analysis

[redacted]

Physical address: [redacted]

Tel:

Email: [redacted]

Pharmacokinetics

[redacted]

Physical address:

[redacted]

Postal address:

[redacted]

Tel: [redacted]

Email: [redacted]

Sponsor

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Strasse 173

55216 Ingelheim

Germany

Tel: [redacted]

Fax: [redacted]

Sponsor Contact Person

[redacted]

Senior Medical Advisor

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Strasse 173

55216 Ingelheim

Germany

Tel:

Fax:

Email: [redacted]

Sponsor Statistical Analysis Contact Person

[redacted]

Study statistician
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim
Germany
Tel:
Email:

[redacted]

Monitor

Information on the monitor to the study is contained in the ISF.

♣ The [redacted] will be referred to as [redacted] in this document, as well as in the ICDs for this study.

5. INTRODUCTION

5.1. Background Information

Diclofenac

Diclofenac is a non-steroidal drug with anti-inflammatory and analgesic activity. It inhibits the enzyme cyclooxygenase, and so directly inhibits the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. The topical usage of diclofenac in acute pain conditions is considered well established and is associated with an improved safety profile due the low systemic plasma concentrations [2, 3].

Voltarol

Voltarol® 12 Hour Emulgel 2.32% (diclofenac) Gel is indicated for the local symptomatic relief of pain and inflammation in:

- Trauma of the tendons, ligaments, muscles and joints, e.g., due to sprains, strains and bruises
- Localized forms of soft tissue rheumatism

The marketed reference product Voltarol® 12 Hour Emulgel 2.32% Gel is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, Voltarol® 12 Hour Emulgel 2.32% Gel relieves pain, decreases swelling and shortens the time to return to normal function. In one ankle sprain study (VOPO-P-307), Voltarol® 12 Hour Emulgel 2.32% Gel significantly decreased pain on movement scores versus placebo treated subjects within 3 days of starting treatment, including a subgroup of patients with severe pain. In addition treatment with Voltarol® 12 Hour Emulgel 2.32% Gel also significantly improved ankle joint function within 3 days of beginning treatment [1].

Capsaicin

Capsaicin is a highly selective and potent exogenous agonist for the transient receptor potential vanilloid 1 (TRPV1) receptor. When activated TRPV1 opens transiently and initiates a depolarization mediated by influx of sodium and calcium ions. In the nociceptive (mostly C- and some Aδ-fibers) nerve endings which selectively express TRPV1, capsaicin mediated depolarization results in action potentials, which are transmitted to the spinal cord and brain and are usually reported as warming, burning, stinging or itching sensations. Capsaicin causes an initial excitation of the neurons and a short period of hypersensitivity. This is followed by a refractory period with reduced sensitivity and, after repeated

applications, persistent desensitization and decreased sensitivity to pain. There is also evidence that capsaicin treatment may interfere with substance P synthesis [4].

5.2. Clinical Pharmacokinetics

Capsaicin

In the current Investigator's Brochure (IB), studies examining higher strengths of capsaicin have found that, for a small proportion of patients, low, transient levels of capsaicin can be detected in the systemic circulation [5].

Voltarol

The information provided below is based on the approved product information as per the Summary of Product Characteristic (SPC) of Voltarol® 12 Hour Emulgel 2.32% Gel [1].

Absorption:

The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. After topical application to approximately 400 cm^2 of skin, the extent of systemic exposure as determined by plasma concentration of Voltarol® 12 Hour Emulgel 2.32% Gel (2 applications/day) was equivalent to diclofenac 1.16% gel (4 applications/day). The relative bioavailability of diclofenac (area under the plasma concentration-time curve [AUC] ratio) for Voltarol® 12 Hour Emulgel 2.32% Gel versus tablet was 4.5% on Day 7 (for equivalent diclofenac sodium dose). Absorption was not modified by a moisture and vapor permeable bandage.

Distribution:

Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after application of topical diclofenac to hand and knee joints. Maximum plasma concentrations were approximately 100 times lower than after oral administration of the same quantity of diclofenac, 99.7% of diclofenac is bound to serum proteins, mainly albumin (99.4%). Diclofenac penetrates inflamed areas, preferentially distributing to and persisting in deep inflamed tissues such as joints, where it is found in concentrations up to 20 times higher than in plasma.

Biotransformation:

Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation resulting in several phenolic metabolites, most of

which are converted to glucuronide conjugates. Two of the phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.

Elimination:

The total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min. The terminal plasma half-life is 1 to 2 hours. Four of the metabolites, including the 2 active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a longer half-life, but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.

Characteristics in Patients:

No accumulation of diclofenac and its metabolites is to be expected in patients suffering from renal impairment. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3. Adverse Events, Contraindications and Warnings

As with any medication, the list of adverse events (AEs) will never be exhaustive, and unexpected or very rare AEs not listed in the Product Information could potentially occur.

Diclofenac

- Should be applied only to intact, non-diseased skin and not to skin wounds or open injuries.
- It should not be used with occlusion.
- It should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.

Capsaicin

- Should not be applied near the eyes or to mucous membranes.
- The application site should not be scratched to avoid damage to the skin.
- Additional heat (e.g., sunlight, infrared treatment, heating pads or warm water) should not be applied while using the cream. The heat effect can be intensified through physical activity (sweating). If the heat effect is too intense, use should be discontinued, and cream residue should be removed with cold water or another skin cream.
- Using the cream on a large area of skin should be avoided.

- It should be noted that the heat effect does not occur immediately after the cream has been applied.

Refer to the product information presented in Appendix 15.1.

5.4. Study Rationale

The purpose of this study is to assess the systemic bioavailability of diclofenac in the presence and absence of capsaicin.

Capsaicin has been shown to act as a penetration enhancer (e.g., for indomethacin [6], naproxen [7]) and thus, might improve the penetration rate and absorption of diclofenac. In addition, both substances have different pharmacodynamics properties and complementary mechanisms of action. By combining both substances in a topical formulation, the new combination product will lead to an increased pain relief compared to the respective mono products.

For a more detailed description of the drug profile refer to the current IB [5], which is included in the ISF.

The proposed study in healthy males and females is designed to establish a PK profile for the topically applied test and reference products to evaluate relative bioavailability.

There is some evidence of racial differences in the transcutaneous penetration of chemicals and drug absorption: decreased transcutaneous penetration has been reported in Black people [13]. To take this into account the study population will be stratified 50:50, Caucasian versus Black people. This will allow estimating and comparing PK endpoints by treatment and race. However, bioavailability ratios as intra-individual comparisons are not expected to be influenced by race. To confirm this, a supportive analysis is planned including the stratification factor race in the model.

5.5. Risks and Benefits

Safety measures are instituted to closely monitor subject safety during this clinical study and to assess known risks of the investigational medicinal products (IMPs).

As healthy male and female subjects will be included in this clinical study, they will not directly benefit from participation.

6. STUDY OBJECTIVES

The main objective of this study is to assess the relative systemic bioavailability of diclofenac in the presence and absence of capsaicin by comparing the systemic bioavailability of diclofenac from a combination product (Diclofenac 2% + Capsaicin 0.075% Topical Gel) with two diclofenac only products, Diclofenac Mono Gel 2% and Voltarol® 12 Hour Emulgel 2.32% Gel, following topical administration. A [redacted]

In order to examine potential racial differences in pharmacokinetics (PK), the study population will be stratified 50:50, Caucasian versus Black people. With respect to the main objective, additionally a supportive analysis will be performed to investigate the influence of race on the intra-individual bioavailability ratios.

Refer to Section 11.4 and Section 9 for primary and secondary endpoints/variables.

7. INVESTIGATIONAL PLAN

Bias is limited by strict adherence to the inclusion and exclusion criteria, the use of a randomization schedule and application of the particular study design. All measurement procedures are clearly defined in advance, and consistently and precisely applied.

7.1. Overall Study Design and Plan: Description

7.1.1. Study Design

This will be a multiple-dose, open-label, randomized, 3-period, 3-treatment, 6 sequence (3x3x6) crossover study with topically administered diclofenac 2% (2 g) in the presence and absence of capsaicin 0.075%, in at least 42 healthy male and female subjects (stratified 50:50 Caucasian versus Black people) in a single study center.

The study will comprise:

- Screening period of maximum 21 days.
- Three-treatment periods (each of which will include a multiple-dose period of 7 days [twice daily and only in the morning on Day 7] and two PK profile periods of 12 hours [Day 1] and 24 hours [Day 7]) separated by a wash out period of at least 7 calendar days between the last administration of the IMP in a treatment period and the first administration of IMP in the next treatment period. Clinic stay/visits will be as follows:
    - Subjects will be admitted to the study center on Day -1 and leave the center after the morning dose on Day 2, at least 24 hours after the initial dosing on Day 1
    - Subjects will visit the study center on Days 3 and 4 for the morning dose
    - On Day 5, they will visit the center for PK blood sampling prior to morning and evening dose and will be re-admitted to the study center on the evening of Day 5
    - Subjects will leave the center at least 24 hours after the morning dose on Day 7
- A follow-up visit will occur within 72 hours after completion of the last treatment period of the study.

Before the first administration of IMPs subjects will be randomized to one of 6 treatment sequences stratified by race (Black, Caucasian), i.e., 4 Black and 4 Caucasian subjects will be assigned to each treatment sequence.

7.2. Discussion of Study Design

7.2.1. Treatment Periods and Schedule of Study Assessments

The timing of assessments is displayed in Table 7-1.

The time of dosing commencement may vary for logistical reasons. Actual clock times will vary between subjects, in relation to actual dosing times.

Table 7-1 Schedule of Study Assessments

Assessment	Screening (Day -21 to -1)	Admission	Treatment Period 1			Admission	Treatment Period 2			Admission	Treatment Period 3			Follow-up Visit[1]
		Days -1 & 5	Days 2 - 4	Day 5, 6	Days 1 & 7	Days -1 & 5	Days 2 - 4	Day 5, 6	Days 1 & 7	Days -1 & 5	Days 2 - 4	Day 5, 6	Days 1 & 7	
Informed consent	X													
In-house stay[2]		X			X	X			X	X			X	
Demographic and anthropometric data[3]	X													
Review of inclusion/exclusion criteria	X													
Alcohol and tobacco consumption patterns	X													
Medical and medications history[4]	X	X												
Adverse events and concomitant medication[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[6]	X													
Vital signs[7]	X				X				X				X	X
12-Lead ECG[8]	X													X
Hematology[9]	X													X
Clinical chemistry[10]	X													X
Serology tests[11]	X													
Urinalysis[12]	X													
Pregnancy test[13] (female subjects only)	X	X				X				X				X
Urine screen for drugs of abuse[14]	X	X				X				X				
Urine screen for tobacco use[15]	X													
Alcohol breath test[16]	X	X				X				X				

Assessment	Screening (Day -21 to -1)	Admission	Treatment period 1			Admission	Treatment period 2			Admission	Treatment period 3			Follow-up Visit[1]
		Days -1 & 5	Days 2 - 4	Day 5, 6	Days 1 & 7	Days -1 & 5	Days 2 - 4	Day 5, 6	Days 1 & 7	Days -1 & 5	Days 2 - 4	Day 5, 6	Days 1 & 7	
Randomization					X (Day 1)									
Weighing of the IMP tube[17]		X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration[19]		X[18]	X			X[18]	X			X[18]	X			
PK profile[20]					X				X				X	
Additional PK sampling[21]		X		X		X		X		X		X		
Inspection of IMP application sites by PI[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Overall assessment of tolerability[23]					X (Day 8)				X (Day 8)				X (Day 8)	

ECG = electrocardiogram; IMP = investigational medicinal product; PK = pharmacokinetic

1. Within 72 hours of completion of the last period of the study or, in the case of a subject who took the IMP and was withdrawn or withdrew, within 72 hours of withdrawal/withdrawing from the study.
2. Subjects will be admitted to the study center on Day -1 and the evening of Day 5 and will be discharged after the morning dose on Day 2 and at least 24 hours after last dosing on Day 7.
3. Sex, race, date of birth, age, height and body weight.
4. The recorded medical history will be updated if necessary on admission to treatment period 1.
5. Medication taken before dosing will be entered as history in the screening CRF of the subject.
6. A full physical examination will include the following: Evaluation for jaundice, pallor (anemia), cyanosis, clubbing, edema and lymphadenopathy; skin evaluation; external ophthalmological evaluation, including fundoscopy; ear, nose and throat; cardiovascular assessment; respiratory assessment; abdominal evaluation; musculoskeletal assessment and neurological assessment; other evaluations may be performed as deemed necessary by the Investigator. This will be commented upon in the clinical study report, if applicable. Refer to Section 7.2.7 for follow-up physical examination.
7. Supine and standing systolic and diastolic blood pressure and pulse will be recorded at screening and at the follow-up visit. Supine blood pressure and pulse will be recorded before administration of IMP; in addition, supine blood pressure and pulse will be recorded at 2, 4 and 6 hours post-dose (Days 1 and 7). Body temperature will be recorded at screening and before administration of IMP (morning dose).

8. Standard 12-lead ECG will be performed at screening and at the follow-up visit.
9. Hematology (ethylenediaminetetraacetic acid [EDTA tubes]): white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelets.
10. Clinical chemistry (Serum separator tubes [SST]): Potassium, sodium, urea, creatinine, uric acid, calcium, protein, albumin, total bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and glucose.
11. Tests for human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C, performed using commercially available test kits. Pre- and post-test counseling will be provided as appropriate.
12. Urinalysis (dipstick): Glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite and leucocytes. Abnormal urinalysis results may be repeated at the discretion of the Investigator. All results will be reported.
13. Serum pregnancy test (quantitative β-HCG [beta human chorionic gonadotropin] method) at screening. On admission to each treatment period (Day -1 each period) urine pregnancy testing will be performed. If any of these tests are positive, subjects will not be allowed further participation in the study. Urine pregnancy test at the follow-up visit.
14. Using a rapid, one-step screening test for simultaneous, qualitative detection of multiple drugs and drug metabolites, such as amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (phenylcyclohexalpiperidine), tetrahydrocannabinol, methadone, methamphetamine, tricyclic antidepressants, oxycodone and propoxyphene. Subjects with alleged false positive test results will be excluded from the study. However, a positive test may be repeated once at the discretion of the Investigator.
15. Cotinine testing using commercially available testing procedures.
16. Alcohol breath test using a portable breath alcohol measuring device. The test will be performed at screening, on admission to each treatment period and at random. If any of these tests are positive, subjects will not be allowed further participation in the study.
17. The tubes will be weighed before and after dosing, whenever the subject is at the study center.

[redacted]

19. IMP will be self-administered in the morning and evening (12 hours apart) on Days 1 to 6 and only in the morning on Day 7. Refer to Section 7.2.6 for window allowance.
20. Blood for PK analysis will be collected on Day 1 at the following time points: 0 hours (prior to morning dose) and at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose (prior to evening dose) (total: 10 samples per treatment period) and on Day 7 pre-dose at 0 hours and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours post-dose (15 samples per treatment period). PK sampling should take preference over other assessments.
21. Additional blood samples to establish attainment of steady state will be collected on Days 5 and 6 (prior to morning dose and evening dose).
22. Inspection of IMP application sites will be done at screening, before every IMP administration and post-dose at 1 and 6 (± 9) hours on Day 1 and Day 7, respectively. On Days 2 to 5 inspections will be done before IMP administration during the morning visit to the clinic (subjects will still be in the clinic the morning of Day 2) and on Day 6 inspection will be done before IMP administration, in the morning and evening, respectively.

23. Assessment will be done before discharge on the morning of Day 8. Refer to Section 9.1.2 and Appendix 15.2.

7.2.2. Safety and Data Monitoring Committees

No safety and data monitoring committee has been established for this study.

7.2.3. Interim Analyses

No interim analyses will be performed in this study.

7.2.4. Expected Duration of Study

The duration of this study is expected to be approximately 38 days per subject (excluding the screening period). The actual overall study duration and study recruitment time may vary.

7.2.5. Screening

Within 21 days before the first administration of IMP and after written informed consent is obtained, screening procedures will be performed on each potential subject (see Table 7-1). Subjects who meet the inclusion criteria (Section 7.3.1) will be considered eligible to participate in the study. Subjects who meet one or more of the exclusion criteria (Section 7.3.2) will not be considered eligible to participate in the study.

At the discretion of the PI, vital signs and laboratory investigations of variables outside the reference ranges may be repeated up to 3 times. Should the variables return to within the reference range, or should the PI consider the variable to be at an acceptable level in relation to the reference range, the persons will be considered eligible to participate in the study.

7.2.6. Treatment Periods

Each treatment period will include a profile period of 12 hours on Day 1 and 24 hours on Day 7 and dosing twice daily on Days 1, 2, 3, 4, 5 and 6 and only in the morning on Day 7.

Subjects will be admitted to the study center on Day -1 and on the evening of Day 5.

Details on the requirements for storage of IMP at home, instructions on administration of IMP and completing of the diary card will be communicated to the subjects in an information leaflet.

Training of Self-administration

IMP will be self-administered. Subjects will be trained by the study staff on Day -1 of each treatment period to administer the IMP on one of the upper thighs. An area of about 20 cm^2 will be marked with a black skin marker pen.

One thigh should be used during the study. During one treatment period (out of 3) one thigh MUST be used. If this is not possible for safety reasons, then the patient will be discontinued.

If, after one period the subject suffers from skin irritation or non-intact skin (e.g., due to injury) the other thigh may be used for the following period.

The IMP will be administered twice (morning and evening) on Days 1 and 6 (12 hours ± 10 min), twice on Days 2 to 5 (12 hours ± 120 min) and in the morning only on Day 7. Each IMP administration will be recorded on a diary card.

Patients will be equipped with disposable gloves and instructed to wear them whenever applying the IMP. An area of approximately 20 cm x 20 cm (corresponding to approximately 2 hand sizes) will be treated. A gel drop of approximately the size of a hazelnut will be applied to the subject's gloved hand and quickly massaged into the skin until the whole amount of gel is absorbed. Each subject will have a new tube assigned per treatment period. The tubes will be weighed before and after dosing, whenever the subject is at the study center and the application site will be inspected by the Investigator at these time points as well. Refer to Schedule of Study Assessments in Table 7-1.

Showering/bathing should be avoided for at least 1 hour before and after the application. External heat and/or occlusive dressings should not be applied to treated area. Wearing of clothing or covering the application area with clothes and/or blankets should be avoided for at least 10 minutes after applying the gel. Also refer to Section 5.3 and Section 7.2.10.1.

Before dosing on Day 1 and Day 7, an indwelling venous cannula will be inserted. The medical staff will decide when to remove or replace the venous cannula based on the time (since insertion of the cannula) or if clotting occurs. If the cannula is removed, the subsequent blood samples will be collected by venipuncture or the cannula will be replaced.

The cannula will be removed before discharge on Day 1 and Day 8 or as needed when not functioning properly any more as stated above.

Food and beverages restrictions are described in Section 7.2.10.2.

Subjects will be allowed to leave the study center at least 24 hours after administration of the first dosing of IMP on Day 1 and at least 24 hours after the last dosing on Day 7.

7.2.7. Follow-up Evaluations

See Table 7-1.

At the discretion of the PI, a follow-up physical examination will be performed on subjects withdrawn from the study due to an AE.

Follow-up laboratory investigations with variables outside the reference ranges will not necessarily be repeated to establish if and when those variables returned to within the reference ranges. The variables will be reviewed against the clinical background, other relevant investigations and their relevance to the administered IMP, before a decision will be made to repeat the investigations in question. At the discretion of the PI, the investigations of certain variables outside the reference ranges may be repeated until the variables return to within the reference range for the particular laboratory test, or until the PI considers the repeated variable to be at an acceptable level in relation to the reference range. If the Investigator has made every effort to contact the subject, but he/she remains unavailable to attend the clinic for repeat of applicable laboratory investigations, the Investigator may declare him/her lost to follow-up.

In cases where results of follow-up evaluations are reported after the database has been locked, the applicable clinical laboratory reports will be presented in the appendices to the clinical study report (CSR).

7.2.8. Sampling, Interim Handling and Storage

7.2.8.1. Safety Blood and Urine Samples

Refer to Table 7-1.

Before starting the study, the Investigator (or designee) will supply the Sponsor with the reference ranges and units of measurement for the laboratory safety variables to be used during the study. If the reference ranges change during the course of the study, the Investigator (or designee) must provide the Sponsor with a list of the new reference ranges and the effective dates.

All safety blood and urine sampling will be performed by the study center, according to [redacted] standard operating procedures (SOPs).

The PI 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.

7.2.8.2. Pharmacokinetic Blood Samples

Pharmacokinetic blood samples will be collected as indicated in the Schedule of Assessments (Table 7-1). The actual blood sampling times will be recorded on source data/ClinBase™ and attached to the case report forms (CRFs).

Venous blood samples, 2 mL for the determination of diclofenac and 4 mL for the determination of capsaicin concentrations, will be collected into labeled potassium-ethylenediaminetetraacetic acid plastic (K_2-EDTA) tubes.

If not processed immediately, blood samples are to be placed on ice between sample collection and centrifuging. Within one hour 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 2 aliquots (of at least 0.8 mL plasma each for capsaicin and 0.4 mL each for diclofenac) and transferred to labeled, plastic tubes and frozen immediately.

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 -20ºC in a temperature mapped freezer until transfer to [redacted] Bioanalytical Services Division (BASD). The labels of sample plasma tubes for capsaicin will be labeled similarly, but will not reflect the treatment period in order to keep the blind in the bioanalytical laboratory. Pooled samples for concentration range estimation will be prepared according to [redacted] SOPs. These specificity 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.

Unused duplicate plasma PK samples will be stored at BASD for 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.

7.2.9. Blood Volume

The total blood volume to be collected from each subject during the study is indicated in Table 7-2.

Table 7-2 Total Blood Volume to be Collected During the Study

Assay	Volume per sample (*mL*)	Total number of samples	Number of treatment periods	Total blood volume (*mL*)
Diclofenac (Day 1)	2	10	3	60
Capsaicin (Day 1)	4	10	1	40
Diclofenac (Days 5,6 and 7)	2	15 + 2(2)	3	114
Capsaicin (Days 5, 6 and 7)	4	15 + 2(2)	1	76
Hematology	4	2		8
Clinical chemistry*	5	2		10
Total blood volume (entire study)**				308

* Serum pregnancy tests (females only) and serology tests at screening will be performed on the sample collected for clinical chemistry

** Excluding repeat laboratory investigations

7.2.10. General and Dietary Restrictions

7.2.10.1. Posture

The IMP will be self-administered as described Section 7.2.6. On Days 1 and 7, after dosing the subjects will remain in the supine position for 10 minutes before covering the dosing area with either clothing or blankets. Except for bladder voiding and ingestion of meals (where applicable), subjects will remain recumbent until 2 hours after administration of study medication, after which no restrictions concerning posture or movement will apply. Posture control procedures will be documented (see Source Data Agreement). For the application of the IMP at home and at the clinic on the other days the subjects will wait 10 minutes before covering the dosing area with either clothing or blankets, with no restrictions on posture or movement.

7.2.10.2. Diet

The ingestion of food and beverages containing citrus fruits and/or apple or pineapple will not be allowed for 72 hours before the administration of IMP and until the last PK blood sample is collected per treatment period.

The ingestion of food and beverages containing alcohol and/or methylxanthines e.g., caffeine (coffee, tea and cola) will not be allowed for 24 hours before the administration of IMP and until the last PK blood sample is collected per treatment period.

Food and beverage intake during the clinic stay will be standardized per treatment period. Meals taken during the clinic stay will be standardized in regard to composition and time of administration (see Source Document Agreement).

Water is allowed as desired. Food and beverage intake will be allowed *ad libitum*, unless restrictions apply, after the subjects have been discharged from the clinic.

7.2.10.3. Physical Activity

Strenuous physical activity will not be allowed for 24 hours before the administration of study medication and until the last PK blood sample was collected per PK profile period.

7.2.10.4. Special Precautions

Subjects will be informed verbally by the Investigator and in writing by way of the ICD of the AEs that they may experience after taking the IMP.

7.3. Selection of Study Population

The criteria are set to ensure a homogeneous subject population without accompanying diseases interfering with the conduct and scientific evaluation of the study. The study population will be stratified 50:50 Caucasian versus Black people. Additionally, the criteria have been selected to minimize risk to the subject's well-being.

7.3.1. Inclusion Criteria

1. Healthy males and females, 18 to 50 years (inclusive) at time of screening.
2. Body mass index (BMI) between 18.5 and 29.9 kg/m^2 (inclusive).
3. Body mass not less than 50 kg for males and females.
4. Findings for medical history, vital signs, physical examination, standard 12-lead electrocardiogram (ECG) and laboratory investigations must be normal or within laboratory reference ranges for the relevant laboratory tests, unless the PI considers the deviation to be not clinically significant for the purpose of the study.
5. Non-smokers.
6. Females, if:
    - Not of childbearing potential, e.g., has been surgically sterilized, undergone a hysterectomy, amenorrhea for ≥ 12 months and considered post-menopausal,

Note: In post-menopausal women, the value of the serum pregnancy test may be slightly increased. This test will be repeated to confirm the results. If there is no increase indicative of pregnancy, the female will be included in the study.

- Of childbearing potential, the following conditions are to be met:
  - Negative pregnancy test.

    If this test is positive, the subject will be excluded from the study. In the rare circumstance that a pregnancy is discovered after the subject received IMP, every attempt must be made to follow her to term.
  - Not lactating.
  - Abstaining from sexual activity (if this is the usual lifestyle of the subject) or must agree to use an accepted method of contraception, and agree to continue with the same method throughout the study.
  - In this study the concomitant use of hormonal contraceptives is allowed.
  - Examples of reliable methods of contraception include oral (documented that the dose has been stable for at least one month before the first intake of the IMP), injectable or implantable contraceptives, non-hormonal/hormonal intrauterine device, and barrier methods combined with an additional contraceptive method.
  - Other methods, if considered by the PI as reliable, will be accepted.

7. Written informed consent given for participation in the study.

7.3.2. Exclusion Criteria

1. Evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study or limit the ability to comply with protocol requirements.
2. Current alcohol use > 21 units of alcohol per week for males and > 14 units of alcohol per week for females. One unit (10 g alcohol) is equal to beer (330 mL), wine (200 mL), or distilled spirits (25 mL) per day.
3. Regular exposure to substances of abuse (other than alcohol) within the past year.
4. Use of any medication, prescribed or over-the-counter (especially products containing diclofenac or use of other oral nonsteroidal anti-inflammatory drugs [NSAIDS]) or herbal remedies, within 2 weeks before the first administration of IMP except if this

will not affect the outcome of the study in the opinion of the PI (in collaboration with the Sponsor). In this study the concomitant use of hormonal contraceptives is allowed.

5. Participation in another study with an experimental drug, where the last administration of the previous IMP was within 8 weeks (or within 5 elimination half-lives for chemical entities or 2 elimination half-lives for anti-bodies or insulin), whichever is the longer before administration of IMP in this study, at the discretion of the PI.
6. Treatment within the previous 3 months before the first administration of IMP with any drug with a well-defined potential for adversely affecting a major organ or system.
7. A major illness during the 3 months before commencement of the screening period.
8. History of hypersensitivity or allergy (acute rhinitis, angioedema, urticaria or bronchial asthma) to the IMP or its excipients or any related medication (Aspirin or any other NSAID).
9. History of hypersensitivity or allergy to cayenne pepper or other capsaicinoids (paprika plants).
10. History of bronchospasm or bronchial asthma, arterial hypertension, myocardial infarction, thrombotic events, stroke, congestive heart failure, impaired renal function or liver disease.
11. History or current diagnosis of gastrointestinal bleeding or peptic ulcer disease.
12. Elevated transaminases (ALT and AST) at screening.
13. History of convulsions.
14. History of porphyria.
15. Relevant history or laboratory or clinical findings indicative of acute or chronic disease, likely to influence study outcome.
16. Donation or loss of blood equal to or exceeding 500 mL during the 8 weeks before the first administration of IMP.
17. Diagnosis of arterial hypotension made during the screening period.
18. Diagnosis of hypertension made during the screening period or current diagnosis of hypertension.

19. Resting pulse of > 100 beats per minute or < 40 beats per minute during the screening period, either supine or standing.
20. Positive testing for HIV, Hepatitis B and/or Hepatitis C.
21. Positive urine screen for drugs of abuse. In case of a positive result, the urine screen for drugs of abuse may be repeated once at the discretion of the PI.
22. Positive cotinine test.
23. Positive pregnancy test.
24. History of any bleeding or blood clotting disorders.
25. History or active severe skin diseases.
26. Immunization using a live organism vaccine within 4 weeks before the first dosing of IMP.
27. Any specific investigational product safety concern.
28. Vulnerable subjects, e.g. persons in detention.
29. Bruises, damaged skin, eczema or wounds on the application site, or the application site inappropriate for applying the IMP in the opinion of the PI.

7.3.3. Withdrawal Criteria

Subjects have the right to withdraw from the study at any time, irrespective of the reason, without detriment to their medical care.

The following are pre-defined incidents that may lead to withdrawal from further participation at the discretion of the PI, and are optional withdrawal criteria:

1. AEs at the discretion of the PI.
2. Intercurrent illness requiring medication. The decision whether or not to withdraw the subject will be at the discretion of the PI and will depend on the nature of the illness and medication used.
3. Protocol violation by subjects, at the discretion of the PI. Protocol violation is defined as the willful disobeying of protocol instructions which have been communicated to the subjects verbally and in writing.

The following are pre-defined incidents that will lead to withdrawal from further participation and are mandatory withdrawal criteria:

4. Pathologically raised oral body temperature, above 38.0ºC, before morning dose of IMP administration on profile days.
5. Positive testing for pregnancy during the study.
6. Positive testing for drugs of abuse during the study.
7. Positive alcohol breath test during the study.
8. Skin irritation of such magnitude that dosing is not possible at IMP application site of the marked thigh during a specific period (the other thigh may be used in another period if needed).
9. If the subject withdraws consent.

The primary reason for treatment discontinuation will be documented (see Source Document Agreement).

If the PI withdraws a subject from treatment or if a subject declines further participation, a follow-up visit will be completed for those who were exposed to IMP, within 72 hours of withdrawal/withdrawing from the study.

If a subject's reason for discontinuation is an AE, this must be reported in accordance with the procedures detailed in Section 12. The Investigator must make every effort to contact a subject before he/she can be regarded as lost to follow-up.

7.3.4. Replacement of Subjects

Subjects who withdraw or are withdrawn from the study will not be replaced, unless fewer complete the study than the estimated required number of evaluable subjects (see Section 11.2).

If a subject is replaced, the replacement will be allocated the subject number of 500 plus the subject number being replaced (e.g., Subject [redacted] will be replaced by [redacted]). 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.

7.3.5. Premature Termination of the Study

The Sponsor or the PI has the right to terminate the study at any time for medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is prematurely terminated for any reason, the Investigator will promptly inform the subjects and will ensure appropriate therapy and follow-up for them. The IEC and the MCC will be informed as soon as possible after the decision has been made to terminate the study and the reasons for termination.

Should the study be prematurely terminated, the completed and partially completed CRFs and remaining IMP must be destroyed locally in agreement with the Sponsor.

A list of [redacted] SOPs governing these actions will be contained in the ISF.

8. TREATMENTS

8.1. Products to Be Administered

Subjects will receive either the test or reference products, according to the randomization schedule. Subjects will receive multiple doses of the test or reference products in 3 different treatment periods.

8.2. Identity of Investigational Medicinal Products

Test Product 1* (A):

Generic name	:	Diclofenac sodium
Trade name	:	Diclofenac mono gel 2%
Dosage form	:	Immediate release topical gel
Dose	:	Multiple doses (2 g, bid) of Diclofenac 2%
Route of administration	:	Topical
Manufacturer	:	Boehringer Ingelheim Pharma GmbH & Co. KG
Country of origin	:	Germany

Test Product 2* (B):

Generic name	:	Diclofenac + Capsaicin
Product name	:	Combination of Diclofenac 2% + Capsaicin 0.075% formulation
Dosage form	:	Immediate release topical gel
Dose	:	Multiple doses (2 g, bid) of Diclofenac 2% + Capsaicin 0.075%
Route of administration	:	Topical
Manufacturer	:	Boehringer Ingelheim Pharma GmbH & Co. KG
Country of origin	:	Germany

Reference Product (C):

Generic name	:	Diclofenac sodium topical gel
Trade name	:	Voltarol® Emulgel 2.32% Gel
Dosage form	:	Immediate release topical gel
Dose	:	Multiple doses (2 g, bid) of Voltarol (Diclofenac sodium

* The sample used in this study is from a validation batch.

		2.32%)
Route of administration	:	Topical
Manufacturer	:	Novartis Consumer Health UK Ltd.
Country of origin		United Kingdom

8.2.1. Identification of Investigational Medicinal Products

The Sponsor will conduct drug identification and content assay for the test products and, if possible, for the reference product. Certificates of analysis will be provided in the CSR.

8.2.2. Supply and Storage

The Sponsor will supply sufficient quantities of all products suitably packed for random choice of IMP for dosing. The PI or designee will ensure that the IMPs are stored in a limited access area according to the storage instructions supplied by the Sponsor which is; store between 2-25ºC, excursions permitted to 26-33ºC for not more than 14 days. The PI or designee will report any relevant deviations from the storage conditions to the Sponsor immediately.

8.2.3. Investigational Medicinal Product Accountability

The PI or designee will ensure that records of the receipt and administration of the IMP are kept and that the IMP will not be used for purposes other than as directed by the clinical study protocol. Once the clinical phase of the study has been completed or prematurely terminated, and after drug accountability has been performed, unused IMPs will be destroyed locally in accordance with Sponsor requirements. If incinerated, the certificate of incineration will be filed in the ISF.

8.2.4. Retention Samples

The Sponsor will retain IMP samples in accordance with the EU Guidelines to Good Manufacturing Practice (GMP), Annex 13 – Investigational Medicinal Products, 03 February 2010.

8.2.5. Labelling and Packaging

The IMPs will be supplied by the Sponsor packaged in 50 g tubes.

Each tube will be labeled, by the Sponsor, with a medication number. Test Product 1 will have numbers 101 to 184. Test Product 2 will have numbers 201 to 284. The Reference Product will have numbers 301 to 384.

Each subject will use a new tube per treatment period.

8.3. Method of Assigning Subjects to Treatment Groups

A randomization schedule will be provided by [redacted] Biostatistics. The randomization schedule will be generated utilizing the PROC PLAN procedure of SAS® software.

Forty-eight subjects will be randomized to a 6 sequence Williams square design for 3 periods and 3 treatments: ABC, BCA, CAB, CBA, ACB, BAC. Subjects will be randomized to 1 of 6 treatment sequences balanced over race. Thus, of each race, 4 subjects will be allocated to a particular sequence.

Subjects will be assigned randomization numbers 001 – 048.

The tubes (and thus medication numbers) will be randomly selected during dosing.

Possible replacements will be handled according to Section 7.3.4.

Blinding is described in Section 8.6.

8.4. Selection of Doses in the Study

In compliance with bioavailability guidelines, the dosage in this study will include multiple topical doses of 2 g (as diclofenac) in 3 treatment periods.

See Section 5 and Appendix 15.1.

8.5. Selection and Timing of Dose for Each Subject

Subjects will receive Test Product 1, Test Product 2 or the Reference Product (according to the randomization schedule).

See Section 7.2.6.

8.6. Blinding

This is an open-label, laboratory-blind study. Access to the randomization schedule will be restricted to assigned study staff members of [redacted] Biostatistics and [redacted] Pharmaceutical Services, as well as the PI and designee. Study staff members of BASD are not allowed access to the randomization schedule until after statistical analysis of the study results. Refer to Section 7.2.8.2 for the handling of capsaicin samples for the protection of the blind. The final statistical analysis will be done according to the Statistical Analysis Plan

(SAP) that will be finalized before database lock and will be based on data following database lock.

8.7. Prior and Concomitant Medication

Subjects must refrain from using any medication, prescribed or over-the-counter (especially products containing diclofenac or use of other oral NSAIDs) or herbal remedies (including St. John's wort [*Hypericum perforatum*]), for 2 weeks before the first administration of IMP and for the duration of the study.

In this study, the concomitant use of hormonal contraceptives is allowed.

Concomitant use of other topical products, including sunscreens, cosmetics, lotions, moisturizers, insect repellants or other topical medications is not allowed anywhere on the body, except on the face. **Concomitant use with oral NSAIDs or Aspirin is also not allowed.**

The administration of concomitant medication will be handled on a case-by-case basis at the discretion of the PI. If any medication is required during the course of the study, it must immediately be reported to the PI. Where medication is taken or needs to be taken, a decision whether to continue or discontinue the subject's participation in the study will be based on safety concerns, the time of medication administration and the possible influence of the ingested medication on the PK of the IMP and interference with the assay method.

8.8. Treatment Compliance

To ensure treatment compliance, the IMP will be administered by the subject himself/herself, for all doses on the same marked area on the same thigh each time as far as possible. Refer to Section 7.2.6 and Section 7.3.3.

9. PHARMACOKINETIC ENDPOINTS AND SAFETY VARIABLES

9.1. Pharmacokinetic and Safety Measurements

Refer to Section 7.2.1 for Schedule of Assessments.

[redacted]

9.1.2. Overall Assessment of Tolerability

Refer to Table 7-1 for timing of assessments.

The subject will assess the overall tolerability of the trial treatment on a 4-point verbal rating scale, see Appendix 15.2. The PI will make the corresponding assessment at about the same time as the subject. Assessments will be made independently from each other, i.e., without knowing the other's assessment result when making the assessment.

9.2. Appropriateness of Measurements

Standard measures to assess PK and safety apply during the study. As this is a bioavailability study, the planned safety measurements are considered to be adequate because the safety of the IMP has been proven by the innovator.

9.3. Drug Concentration (Pharmacokinetic) Measurements

9.3.1. Pharmacokinetic Endpoints

Refer to Section 11.4.

9.3.2. Pharmacokinetic Sample Collection, Sample Handing and Storage

Refer to Section 7.2.8.2.

9.3.3. Pharmacokinetic Drug Assays

The Clinical Laboratory of [redacted] BASD is accredited according to the International Organization for Standardization/the International Electrotechnical Commission 17025 Standard. The analytical laboratories of BASD have been inspected for their compliance with Good Laboratory Practice (GLP), based on the Organization for Economic Cooperation and Development guidelines ENV/MC/CHEM (98)17 revised in 1997. These inspections have confirmed that the laboratory is able to successfully apply GLP principles in studies that are performed at BASD. Analytical methods are validated according to internationally accepted standards (as per European Medicines Agency [EMA] guideline for Bioanalytical Method Validation). The quality and integrity of the analytical work generated in this study are evaluated according to the acceptance criteria, as described in the SOPs of [redacted] BASD.

Quantitative analysis of diclofenac and capsaicin in the collected plasma samples will be performed by BASD using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

The pure substances with a certificate of analysis of diclofenac and capsaicin will be supplied by the Sponsor. Alternatively, [redacted] BASD will purchase the pure substances from trustworthy suppliers on behalf of the Sponsor. These pure substances will be used as analytical standards for the preparation of calibration standards that are required for the quantitative analysis of diclofenac and capsaicin.

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

Complete method validation and bioanalytical reports will be provided.

10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

A study initiation meeting chaired by the PI or designee will be held before study commencement.

10.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The site will allow the study monitor and Sponsor representatives' direct access to all study documents, medical files, and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the study center.

10.2. Audit/Inspections

The Investigator site, facilities and all data and documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The Investigator must allow the auditor/inspector/any representatives of regulatory authorities access to all relevant documents and be available to discuss any findings/issues. An audit certificate will be included in the CSR if an audit was performed.

10.3. Study Monitoring

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.

10.4. Data Collection

[redacted] Data Management will provide a CRF to be completed for each subject. The entries will be checked by trained personnel. Errors or inconsistencies will be corrected. Any changes or corrections to a CRF will be dated, initialed and explained (if necessary) and will not obscure the original entry (e.g. correction fluid or covering labels must not be used). An explanation for the omission of any required data will appear on the appropriate page. The Investigator will sign the completed CRF, thereby taking responsibility for the accuracy of the data in the entire CRF. The Investigator will retain records of the changes and corrections.

Source data will be defined as such in the Source Document Agreement. The study center's electronic data capture and process control system may be used, as indicated in the Source Document Agreement.

The responsible study monitor will check data at the monitoring visits to the study center (see Section 10.3). The Investigator will ensure that the data collected are accurate, complete and legible.

All clinical work conducted under the clinical study protocol is subjected to GCP regulations. These include an inspection by the Sponsor and Regulatory Authority representatives at any time. The Investigator will agree to the inspection of study-related records by Regulatory Authority representatives and to audits of the Sponsor or third parties named by the Sponsor (also see Section 10.2).

10.5. Data Management

[redacted] 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) may 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.

Appropriate data validation checks may be developed based on the data sources. A data validation specification (DVS) may be created if existing standard checks alone are not adequate. In such case, study-specific DVS will be created incorporating standard and custom checks that are already available. If applicable, the DVS must be finalized before data validation.

After the data had been monitored, they will be transferred to [redacted] Data Management, and all CRFs received will be logged and filed.

Data will be entered from completed paper CRFs into the clinical database by double data entry. Electronic source data will be utilized directly without data entry. Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

The raw data intended for further processing will be checked by standard routines or according to the study DVS and queries will be generated and sent on the data clarification

forms (DCFs) to the Investigator for response. Appropriate corrections to the data will be made based on the responses on the signed DCFs. This process will be repeated until no further discrepancies are found. The data will be then be declared as clean. Applicable documentation will be stored in the study files.

11. STATISTICAL METHODS

11.1. Statistical Methodology

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 CSR.

The tables, figures and listings that will be provided are detailed in the SAP.

11.1.1. Pharmacokinetic Population

The PK population will consist of all subjects in the safety population for whom at least one of area under the plasma concentration-time curve over one dosing interval ($AUC_{0-\tau,ss}$ [τ = 12 hours]) or maximum steady-state plasma drug concentration during a dosage interval ($C_{max,ss}$) can be calculated for one treatment and who have no major protocol deviations thought to impact on the analysis of the PK data.

11.1.2. Safety Population

All subjects who received at least one dose of IMP will be included in the safety analysis for the study.

11.2. Determination of Sample Size

Up to 48 eligible subjects will be entered into the study to complete the study with at least 42 evaluable subjects.

The sample size determination is not based on a power calculation, but to assure a precise estimation of relative bioavailability ratios with respect to AUC_{ss} and $C_{max,ss}$. Precision is defined as the ratio of upper to lower confidence interval (CI) limit and can also be shown in terms of the width of CIs (note that the precision is independent of the actual ratio of geometric means [gMeans] but CIs are not as can be seen in the table below).

Different estimates of the geometric coefficient of variation (gCV) for AUC and C_{max} values of topical diclofenac were found in literature [9] regarding AUC_{ss} and $C_{max,ss}$ of PENNSAID topical solution and [10] regarding C_{max} and AUC_{0-24} of Voltaren topical gel. There, variability was very high, gCVs were calculated from CIs of ratios which ranged from 21 to

41 % and even 57% in one case. Based on this data, a gCV of 40% was used for estimation of precision for different scenarios.

Assuming an intra-individual variability of 40% for both AUC_{ss} and $C_{max,ss}$, the trial will need N=42 analyzable subjects in order to achieve two-sided 90% CIs meeting a precision of 1.42 with a probability of 95%.

Table 11-1 Expected Two-sided 90% Confidence Intervals for Different Ratios T/R and gCVs for a Sample Size of 42, Coverage Probability = 95%

gCV [%]	T/R	90% CI	Precision upper CL/lower CL
40	0.95	80 - 113	1.41
	1.00	84 - 119	1.42
	1.05	88 - 125	1.42
45	0.95	78 - 115	1.47
	1.00	83 - 121	1.46
	1.05	87 - 127	1.46

The calculation was performed as described by Julious [11, Section 7.2] and Elashoff [12].

11.3. Protocol Deviations and Changes to Planned Analyses

Permission from the Sponsor in writing will be obtained should any changes be required to the clinical study protocol and a protocol amendment will then be drawn up to be submitted to the regulatory authorities. No waivers will be accepted. Should the safety of the subjects necessitate immediate action, which represents a deviation from the clinical study protocol, the Sponsor will be informed as soon as possible.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis populations for the study.

Protocol deviations and changes to planned analyses will be described in the CSR.

For protocol amendments, see Section 3.1.

11.4. Pharmacokinetic Endpoints

Calculation of the PK endpoints will be made with Phoenix® WinNonlin® 6.2 (or higher) (Certara, L.P., 1699 South Hanley Road, St Louis, Missouri 63144, USA).

The PK endpoints will be calculated for each subject and treatment using non-compartmental analysis and using the actual sampling time points (relative to IMP administration).

Steady state will be confirmed by visual inspection of a graph of the pre-dose samples on Days 5, 6, and 7.

[redacted]

Additionally, samples with relevant time deviations may be excluded from statistical analysis. Such deviations which may impact accurate calculations of PK parameters will be reviewed at the data review meeting (DRM). In all cases, the data will be reported in the CSR listing.

11.4.1. Primary Pharmacokinetic Endpoints

Primary and secondary endpoints are only calculated for diclofenac.

- Area under the plasma concentration-time over one dosing interval (τ = 12 hours) ($AUC_{0-\tau,ss}$) (Day 7)
- $C_{max,ss}$ obtained directly from the concentration-time data (Day 7)

11.4.2. Secondary Pharmacokinetic Endpoints

- Time to maximum observed plasma concentration at steady state ($t_{max,ss}$) (Day 7)
- Average plasma concentration ($C_{av,ss}$) calculated as $AUC_{0-\tau,ss}/\tau$, τ is one dosing interval (12 hours)
- Percentage peak-trough fluctuation (%PTF), calculated as $[100*(C_{max,ss} - C_{pre,ss})/C_{av,ss}]$

[redacted]

[redacted]

11.5. Safety Variables

See Section 11.8.

11.6. Presentation of PK Data, Descriptive Statistics and PK Assessment

The actual blood sampling times and time deviations will be listed for each subject dosed, by treatment and scheduled sampling time. Plasma concentrations of diclofenac and capsaicin will be listed and summary statistics (number of subjects [n], arithmetic mean, gMean (geometric mean), median, gCV, coefficient of variation (CV), standard deviation [SD], minimum and maximum) per treatment will be provided. These same summary statistics by treatment and race will be provided.

Concentrations below the lower limit of quantification (LLOQ) will be indicated as below the limit of quantification (BLQ). These BLQ concentrations will be handled as follows:

- For descriptive statistics, BLQ concentrations will not be substituted by zero before the calculation of the summary statistics. Values reported as 'NS' (no sample) will be set to "missing".
- For PK calculations, missing concentrations will be deleted, resulting in an interpolation between the nearest 2 concentration values.
- For PK assessment, all BLQ values at pre-dose and in the absorption phase, before the first reported concentration, will be substituted by zeros. The BLQ values between evaluable concentrations and during the terminal phase will be set to missing, before the calculation of the PK endpoints.
- Concentration data identified with no valid result (NOR) or not analyzed (NOA) are not considered in the evaluation (graphs and calculations). However, they are listed in the respective tables of the CSR.

The PK endpoints of diclofenac and capsaicin will be listed and summary statistics (n, arithmetic mean, gMean, median, gCV, CV, SD, minimum, 10th percentile [P10], 25th percentile [Q1], 75th percentile [Q3], 90th percentile [P90] and maximum) per treatment will be provided. These same summary statistics per treatment and race will be provided.

Descriptive statistics of concentrations at specific time points and PK parameters are calculated by default 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 is based on the total number of samples that were drawn at the specific time point (i.e., BLQ, NOR, and NOA are included).

The individual plasma diclofenac [redacted] concentration versus actual time profiles for each subject and treatment, as well as the mean (arithmetic and geometric) plasma diclofenac [redacted] concentration versus scheduled time profiles for each treatment, will be presented graphically on a linear-linear and log-linear scale. Mean (arithmetic and geometric) plasma diclofenac [redacted] concentration versus scheduled time profiles for each treatment, will be presented graphically on a linear-linear and log-linear scale by race. Individual plasma concentrations will be presented using actual, rather than planned, sampling times. Combined individual concentration versus time graphs per treatment will also be presented on a linear-linear scale, together with the gMean values. The individual log-linear graphs reflecting the WinNonlin modeling results will also be provided.

The data listings, descriptive statistics, statistical analysis and graphs of this study will be generated using SAS® software*.

11.7. Analysis of Relative Bioavailability

Relative bioavailability will be estimated for diclofenac by the ratios of the gMeans (test/reference [T/R]) for AUC and C_{max} at steady state (refer to Section 11.4.1). Additionally, their two-sided 90% CIs will be provided.

The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including fixed effects for sequence, subject nested within sequence, period and treatment. For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). CIs

* SAS® Version 9.2 or higher of the SAS System. Copyright© 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, USA.

will be calculated based on the residual error from ANOVA. The differences between the test and reference product and the CIs will be back-transformed to the original scale, resulting in point estimates of the T/R gMean ratios and 90% CIs.

The following comparisons will apply:

- Test Product 2 vs Reference
- Test Product 2 vs Test Product 1

Only the data for the comparison under investigation will be included in the statistical analysis (i.e., when comparing Test Product 2 and Reference, the data for the Test Product 1 will be removed from the dataset), only subjects with data for both products will be retained in the analysis.

The effect of race on relative bioavailability will be analyzed as supportive analysis, supportive because race is not expected to influence intra-individual bioavailability ratios [14].

The statistical model of the supportive analysis will be an ANOVA on the logarithmic scale including fixed effects for sequence, period, race, treatment, treatment and race interaction and subject nested within sequence and race interaction. The effect of race will be checked

and for each endpoint, least squares means by treatment and race will be tabulated. Point estimates of the T/R gMean ratios and 90% CIs will be presented by race in the same way as for the main analysis.

11.8. Presentation of Baseline Characteristics and Safety Data

Baseline characteristics and safety data will be presented as indicated below.

Demographic and anthropometric data will be listed for all subjects in the safety population. Demographic characteristics will be summarized (n, mean, SD, minimum and maximum for age and BMI; and frequency counts and percentages for race, and sex).

Subject disposition will be listed and summarized including the number and percentage of discontinued subjects and primary reason for discontinuation.

AEs will be coded, listed and summarized by treatment. The coded AEs will also be summarized by System Organ Class (SOC) and preferred term and product; SOC, preferred term, causality and product; and SOC, preferred term, intensity and product. For the tabulations, the AEs will be grouped into 2 categories, namely "Reasonably Related" and "Not Related".

Hematology and clinical chemistry values will be listed and summarized (n, mean, SD, median, minimum, maximum), and urinalysis data will be listed for all subjects in the safety population. Abnormal hematology and clinical chemistry values will be flagged as "L" (for values lower than the lower limit of the reference range) and "H" (for values higher than the upper limit of the reference range). The assessment of the clinical significance will be indicated as "NCS" (abnormal, not clinically significant) or "CS" (abnormal, clinically significant) or "Rep" (whether the test was repeated).

ECGs will be classified as "Normal", "Abnormal NCS", "Abnormal CS" and listed, including changes from baseline. Summary statistics will be provided.

Vital signs will be flagged for measurements that are outside the reference range (low [L] or high [H]) and listed, including changes from baseline. Summary statistics will be provided.

[redacted] and data from inspection of IMP application site will be listed. Inspection results will be reported as normal or abnormal as indicated in the CRF. Based on the DRS, skin reactions will be categorized as positive for scores ≥ 3 and negative for scores < 3. Overall tolerability scores will be listed.

Prior and concomitant medication will be coded and listed separately.

Additional listings will be presented for physical examination, urinalysis, pregnancy testing, serology and drugs of abuse and tobacco use.

12. ADVERSE EVENTS

Each subject will be carefully monitored by the Investigator for AEs. In addition, information on AEs will be obtained from the subjects by study staff regularly questioning them, although no leading questions will be asked. When an AE occurs, the PI will decide whether to withdraw the subject from the study and/or initiate appropriate treatment. After withdrawal from the study, it will be ensured that the subject is given appropriate medical care, if needed, which may take the form of referral to a physician.

In the case of any event requiring medical intervention occurring during the clinic stay, the Investigator will institute general supportive measures including, where necessary, respiratory assistance and cardiopulmonary resuscitation.

12.1. Definitions

12.1.1. Adverse Events

An 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 unfavorable 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 AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off label use, overdose, misuse, abuse and medication errors.

12.1.2. Serious Adverse Events

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

- Results in death;
- Is life-threatening;

Life-threatening in this context refers to an event in which the subject 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 in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Cancers of new histology and exacerbations of existing cancer must be reported as a serious AE regardless of the duration between discontinuation of the IMP and the occurrence of cancer, if the site becomes aware of such an occurrence.

In accordance with the EMA initiative on Important Medical Events, the Sponsor 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 a SAE as given above. A copy of the latest list of "Always Serious AEs" will be provided for reference and filing in the ISF. These events should always be reported as SAEs as described in Section 12.4.

12.1.3. Adverse Events of special interest

The term AEs of special interest (AESIs) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same time frame that applies to SAE, please see Section 12.4.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- An elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities will be followed up according to the drug-induced liver injury (DILI) checklist provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the PI will make sure these parameters are analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist will be followed.

12.2. Classification of Adverse Events

AEs have to be recorded on an AE form in the subject's CRF and graded as mild, moderate, or severe according to the following definitions:

- **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.

12.3. Causal Relationship of Adverse Events

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterized 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 etiologies 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

12.4. Reporting Procedures of Adverse Events/Serious Adverse Events

The PI or designee is responsible for recording in the CRF **all** AEs which have occurred from signed informed consent until individual subject's end of study, regardless of their relationship to the IMP. After the individual subject's end of study the Investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESI of which the Investigator may become aware of.

The Investigator must report SAEs, AESIs and non-serious AEs which are relevant for the reported SAE or AESI on the Sponsor's SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point [redacted] 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.

The residual effect period (REP) for each treatment period in this study is defined as 1 day (24 hours) after trial medication application of the corresponding treatment period.

Information Required

For each AE, the Investigator should provide the information requested on the appropriate CRF 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 AE/SAE in the CRF 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 significant by the Investigator
- Dermal reactions, if they are judged clinically significant by the Investigator
- Abnormal reporting of IMP application site, if judged clinically significant by the Investigator

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All AEs and SAEs including those persisting after individual subjects end of trial must be followed up until they have been resolved, have been sufficiently characterized, or no further information can be obtained. In the event of an SAE, the outcome has to be reported in the CSR, as well as to the PI, Sponsor, monitor, the IEC and the MCC.

Pregnancy

In rare cases, pregnancy may occur in a clinical trial. Once a subject has been enrolled into this clinical trial, and has taken trial medication the Investigator must report immediately (within 24 hours of awareness) a potential drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (fax number: [redacted]

The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the DEDP 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 and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

12.5. Allocation of Adverse Events to Treatment Groups

AEs are allocated to treatment groups 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 are assigned to screening.
- All AEs with start date/time after the date/time of first dosing in period 1, but before dosing in period 2, would be assessed against the treatment received in period 1.
- AEs with start date/time after the date/time of first dosing in period 2, but before dosing in period 3 would be assessed against the treatment received in period 2.
- AEs with start date/time after the date/time of first dosing in period 3 would be assessed against the treatment received in period 3.

With this definition AEs occurring in wash-out are assessed against the treatment received in the preceding period. AEs up to the follow-up visit would be assessed against the treatment received in period 3 if the start date/time of the AE was after dosing in period 3.

12.6. Expedited Reporting of Adverse Events

The Sponsor is responsible for fulfilling their legal regulatory reporting obligation and in accordance to the regulatory requirements.

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Documentation

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures.

Investigator-specific essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents could be retained for a longer period however, if required by the regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained.

Study documentation will be archived by [redacted] for 15 years.

13.2. Publication of Results

If a publication (e.g., in a scientific journal) based on the results of this study is envisaged, approval from the Sponsor will be obtained and a draft manuscript will be submitted to the Sponsor for scrutiny and comment. The choice of conduit will be mutually agreed on by the PI and the Sponsor.

13.3. Sponsor's Obligation

The onus rests with the Sponsor to ensure that the clinical study protocol complies with all their requirements.

13.4. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH Guideline for Structure and Content of CSRs (ICH E3). Copies of the CSR will be provided to the IEC and the MCC in accordance with regulatory requirements and [redacted] SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCES

1. Summary of Product Characteristics. Voltarol 12 hour Emulgel 2.32 % Gel or Voltarol Extra Strength Emulgel 2.32% Gel, revised 20 March 2013.

2. Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults (review). Cochrane Database Syst Rev (9), CD010111 (2012)

3. Zacher J, Altman R, Bellamy N, Bruehlmann P, Silva J da, Huskisson E, Taylor RS. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin 24 (4), 925 - 950 (2008)

4. O'Neill J, Brock C, Olesen AE, Andresen T, Nilsson M, Dickenson AH. Unravelling the mystery of capsaicin: a tool to understand and treat pain. Pharmacol Rev 64 (4), 939 - 971 (2012)

5. Investigator's Brochure, diclofenac and capsaicin, Version 1, dated 19 December 2015

6. Fang JY, Fang CL, Hong CT, Chen HY, Lin TY, Wei HM. Capsaicin and nonivamide as novel skin permeation enhancers for indomethacin. Eur J Pharm Sci 12, 195 - 203 (2001)

7. Degim IT, Uslu A, Hadgraft J, Atay T, Akay C, Cevheroglu S. The effects of Azone and capsaicin on the permeation of naproxen through human skin. Int J Pharm 179, 21 - 25 (1999)

8. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 corr1) (draft XXIII) (London, 21 February 2013, EMA/CHMP/EWP/280/96 rev1). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500140482.pdf (access date: 18 March 2015); London: European Medicines Agency (EMA) (2013)

9. Center for Drug Evaluation and Research, application number 204623Orig1s00. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204623Orig1s000ClinPharmR.pdf. Accessed on May 2016.

10. Center for Drug Evaluation and Research, application number 21-22. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022122_sumr.pdf. Accessed on May 2016.

11. Julious SA. Sample sizes for clinical trials with Normal data. Statist Med 2004; 23:1921–1986.

12. Elashoff JD. nQuery Advisor version 7.0 user's guide. Cork: Statistical Solutions 2007.

13. Alexa B. Kimball. Skin Differences, Needs, and Disorders across Global Populations. J Investig Dermatol Symp Proc (1):2-5 (2008).

14. European Medicines Agency. International Council for Harmonisation Topic E 9. Note for guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96), September 1998

Guidance documentation referred to within the clinical study protocol include, but are not limited to the following:

- Declaration of Helsinki, Fortaleza 2013
- Department of Health, South Africa. Guidelines for Good Practice, 2006
- International Council for Harmonisation Guideline for Good Clinical Practice, 2002
- European Union Directive 2001/20/EC, 04 April 2001
- European Union Directive 2005/28/EC, 08 April 2005
- European Union Directive 2001/83/EC, 06 November 2001
- EudraLex Volume 4 – European Union Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 13 – Investigational Medicinal Products, ENTR/F/2/AM/an D (2010) 3374, 03 February 2010
- Medicines Control Council of South Africa, Biostudies Guideline
- Maintenance of the ICH guideline on clinical safety data management: Data elements for transmission of individual case safety reports, E2B (R2), February 2001
- International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3), 1996
- European Medicines Agency Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1, 2010
- European Medicines Agency Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CPMP/EWP/280/96 Corr1, 2014

15. APPENDICES

15.1. Product Information – Reference Product

Summary of Product Characteristics. Voltarol 12 hour Emulgel 2.32 % Gel or Voltarol Extra Strength Emulgel 2.32% Gel, revised 20 March 2013.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Voltarol 12 Hour Emulgel 2.32% Gel

or

Voltarol Extra Strength Emulgel 2.32% Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diethylammonium-{-o-[2,6-dichlorophenyl)-amino]-phenyl}-acetate.

100g of Voltarol® 12 Hour Emulgel 2.32% Gel contains 2.32g of the active substance diclofenac diethylammonium, which corresponds to 2g diclofenac sodium.

Excipients: Propylene glycol (50 mg/g gel)

Buthylhydroxytoluene (0.2 mg/g gel).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel

White to practically white, soft, homogeneous, cream-like gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the local symptomatic relief of pain and inflammation in:

- trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises
- localised forms of soft tissue rheumatism

4.2 Posology and method of administration

Adults and children aged 14 years and over: Voltarol® 12 Hour Emulgel 2.32% Gel should be rubbed gently into the skin**.** Depending on the size of the affected site to be treated 2-4g (a circular shaped mass approximately 2.0-2.5cm in diameter) should be applied 2 times daily (preferably morning and evening)**.** The maximum daily dose is 8g. Therefore the maximum weekly dose is 56g.

After application, the hands should be washed unless they are the site being treated.
If symptoms persist after 7 days or get worse at any time, medical advice should be sought.
Not to be used for more than 7 days unless recommended by a doctor.
Use in the elderly: The usual adult dosage may be used.
Children and adolescents: There are insufficient data on efficacy and safety available for the children and adolescents below 14 years of age (see also contraindications section 4.3). In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.

4.3 Contraindications

Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

Hypersensitivity to any other ingredient of the gel.

Concomitant use of oral NSAID's.

Voltarol® 12 Hour Emulgel 2.32% Gel should not be co-administered with other products containing diclofenac.

During the last trimester of pregnancy.

4.4 Special warnings and precautions for use

The possibility of systemic adverse events from application of Voltarol® 12 Hour Emulgel 2.32% Gel cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see the product information on systemic forms of diclofenac).

Voltarol® 12 Hour Emulgel 2.32% Gel should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be used with occlusion. It

should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.

Patients with a history of, or active, peptic ulceration. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases.
Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from or with a previous history of asthma or allergic disease.

Discontinue if rash develops.

Information concerning excipients

Voltarol® 12 Hour Emulgel 2.32% Gel contains propylene glycol, which may cause mild, localised skin irritation in some people. It also contains butylhydroxytoluene which may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

Systemic absorption of diclofenac from topical application is very low and no drug interactions during treatment with Voltarol Emulgel have been reported, but the following have been observed with oral forms of diclofenac or other NSAIDs.

Lithium and digoxin: Voltarol may increase plasma concentrations of lithium and digoxin.

Anticoagulants: Although clinical investigations do not appear to indicate that Voltarol has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Antidiabetic agents: Clinical studies have shown that Voltarol can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Ciclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDs, including diclofenac. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Other NSAIDs and steroids: Co-administration of Voltarol with other systemic NSAIDs and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.

Diuretics: Various NSAIDs are liable to inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Anti-hypertensives: Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

4.6 Fertility, pregnancy and lactation

Fertility

Treatment with Voltarol® 12 Hour Emulgel 2.32% Gel is unlikely to have an adverse effect on fertility because the systemic exposure to diclofenac after application of Voltarol® 12 Hour Emulgel 2.32% Gel is low.

Pregnancy

The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition,

increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

The mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of Voltarol® 12 Hour Emulgel 2.32% Gel no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional. Under this circumstance, Voltarol® 12 Hour Emulgel 2.32% Gel should not be applied on the breasts of nursing mothers, nor elsewhere on large areas of skin or for a prolonged period of time (see section 4.4).

4.7 Effects on ability to drive and use machines

Voltarol® 12 Hour Emulgel 2.32% Gel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects include mild and passing skin reactions at the site of application. In very rare instances, allergic reactions may occur.

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: *very common* (≥ 1/10) *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare* (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Very rare: Rash pustular

Immune system disorders Very rare: Hypersensitivity (including urticaria), angioedema
Respiratory, thoracic and mediastinal disorders Very rare: Asthma
Skin and subcutaneous tissue disorders Common: Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus. Rare: Dermatitis bullous. Very rare: Photosensitivity reaction

The following additional side-effects have been observed with oral forms of diclofenac.

Gastro-intestinal tract
Occasional: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).
Rare: Gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhoea.
In isolated cases: Lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.

***Central Nervous System*:**
Occasional: Headache, dizziness, or vertigo.
Rare: Drowsiness, tiredness.
In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing. Tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.

***Skin*:**
Occasional: Rashes or skin eruptions.
Rare: Urticaria.
In isolated cases: Eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), photosensitivity reactions, erythroderma (exfoliative dermatitis), loss of hair, purpura including allergic purpura.

***Kidney*:**
In isolated cases: Acute renal failure, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

***Liver*:**
Occasional: Elevation of serum aminotransferase enzymes (ALT, AST).
Rare: Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood:

In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

***Hypersensitivity*:**
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of rare cases of anaphylactic/anaphylactoid systemic reactions including hypotension, and respiratory tract reactivity comprising
asthma, aggravated asthma, bronchospasm or dyspnoea. (See also "Skin").

***Other organ systems*:**
Rare: Oedema
Isolated cases: Impotence (association with diclofenac is doubtful), palpitation, chest pain, hypertension.

4.9 Overdose

The low systemic absorption of topical diclofenac renders overdose very unlikely.
However undesirable effects, similar to those observed following an overdose of Voltarol tablets, can be expected if Voltarol® 12 Hour Emulgel 2.32% Gel is inadvertently ingested (e.g. 1 tube of 50 g contains the equivalent of 1 g diclofenac sodium.)
In the event of accidental ingestion, resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicines should be used. Gastric lavage and the use of activated charcoal should be considered, especially within a short time of ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Topical products for joint and muscular pain. Anti-inflammatory preparations, non-steroids for topical use, ATC code: M02A A15
Mechanism of action and pharmacodynamic effects:
Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin synthesis is the primary mechanism of action of diclofenac.
Voltarol® 12 Hour Emulgel 2.32% Gel is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of

traumatic or rheumatic origin, Voltarol® 12 Hour Emulgel 2.32% Gel relieves pain, decreases swelling, and shortens the time to return to normal function.
In one ankle sprain study (VOPO-P-307), Voltarol® 12 Hour Emulgel 2.32% Gel significantly decreased pain on movement scores versus placebo treated subjects within three days of starting treatment, including a subgroup of patients with severe pain. In addition treatment with Voltarol® 12 Hour Emulgel 2.32% Gel also significantly improved ankle joint function within 3 days of beginning treatment.
Due to an aqueous-alcoholic base the gel also exerts a cooling effect.

5.2 Pharmacokinetic properties

Absorption
The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. After topical application to approximately 400 cm^2 of skin, the extent of systemic exposure as determined by plasma concentration of Voltarol® 12 Hour Emulgel 2.32% Gel (2 applications/day) was equivalent to diclofenac 1.16% gel (4 applications/day). The relative bioavailability of diclofenac (AUC ratio) for Voltarol® 12 Hour Emulgel 2.32% Gel versus tablet was 4.5% on day 7 (for equivalent diclofenac sodium dose). Absorption was not modified by a moisture and vapour permeable bandage.
Distribution
Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after application of topical diclofenac to hand and knee joints. Maximum plasma concentrations were approximately 100 times lower than after oral administration of the same quantity of diclofenac. 99.7 % of diclofenac is bound to serum proteins, mainly albumin (99.4 %).
Diclofenac penetrates inflamed areas, preferentially distributing to and persisting in deep inflamed tissues such as joints, where it is found in concentrations up to 20 times higher than in plasma.
Biotransformation
Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of the phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.
Elimination
The total systemic clearance of diclofenac from plasma is 263 ± 56 ml/min. The terminal plasma half-life is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a longer half-life but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.
Characteristics in patients
No accumulation of diclofenac and its metabolites is to be expected in patients suffering from renal impairment. In patients with chronic hepatitis or non-

decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

Voltarol® 12 Hour Emulgel 2.32% Gel was well tolerated in a variety of studies. There was no potential for phototoxicity and diclofenac-containing gel caused no skin sensitisation or irritation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene
Carbomers
Cocoyl caprylocaprate
Diethylamine
Isopropyl alcohol
Liquid paraffin
Macrogol cetostearyl ether
Oleyl alcohol
Propylene glycol
Perfume eucalyptus sting
Purified water

6.2 Incompatibilities

None Stated

6.3 Shelf life

Three years

6.4 Special precautions for storage

Do not store above 30°C.
Voltarol® 12 Hour Emulgel 2.32% Gel should be kept out of reach and sight of children.

6.5 Nature and contents of container

Aluminium laminated tube [low density polyethylene / aluminium / high density polyethylene (internal layer)] fitted with a high density polyethylene shoulder and closed by a moulded seal. The tube is closed with a polypropylene screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use.
Pack sizes: 20g, 30g, and 50g
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Novartis Consumer Health UK Ltd.
Trading as Novartis Consumer Health
Watchmoor Park, Camberley Surrey
GU15 3YL
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00030/0447

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/03/2013

10 DATE OF REVISION OF THE TEXT

20/03/2013

[redacted]

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]