

STATISTICAL ANALYSIS PLAN ADDENDUM 1

Sponsor Study Number: 1358.2

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 HOUREMULGEL 2.32% GEL IN AT LEAST 42 HEALTHY MALES AND FEMALES

Version: Final 1.0

Date: 22/Nov/2017

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REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 1.0	20 Oct 2017	[REDACTED]	New document
Draft 2.0	07 Nov 2017	[REDACTED]	Completely revised and provided an overview Table 2
Draft 3.0	21 Nov 2017	[REDACTED]	Implementation of comments and simplification of Table 1 and Table 2
Final 1.0	22 Nov 2017	[REDACTED]	Minor revision

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Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study as presented in this document.

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ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AUC	Area under the concentration-time curve
$AUC_{0-\tau, ss}$	AUC over the dosing interval at steady state
$AUC_{0-\tau, ss, norm\ by\ gel}$	AUC over the dosing interval at steady state normalized to weight of administered gel
BID	Bis in die, twice daily
CSP	Clinical Study Protocol
$C_{max, ss}$	Maximum observed concentration at steady state during the dosing interval
$C_{max, ss, norm\ by\ gel}$	Maximum observed concentration at steady state during the dosing interval normalized to weight of administered gel
IMP	Investigational Medicinal Product
PK	Pharmacokinetic
SAP	Statistical Analysis Plan

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1. STATISTICAL ANALYSIS PLAN ADDENDUM

The Statistical Analysis Plan (SAP) Addendum details the changes and/or additional analyses required that are not currently described in the final SAP Version Final 1.0 dated 08/Sep/2017. The SAP Addendum describes any deviations from the planned analyses, additional analyses and if applicable, new tables, listings and figures that are to be produced.

2. OVERVIEW OF CHANGES REQUIRED

2.1 Changes in structure and content of tables and listings

In appendix 16.1.9.3 the tables will be restructured to show one table per type of analysis, including all analytes in one table, as shown in Table 3 below.

In Listing 16.2.7:1 “Adverse Events”, for clarification, the footnote “Note: An event with outcome of “NOT RECOVERED/NOT RESOLVED” is directly followed by a subsequent event with outcome “RECOVERED/RESOLVED”.” will be added.

In Listing 16.2.5:1 “Exposure to Study Drug” a column for the tube weight difference (g) used for normalization of PK parameters will be added.

In Table 15.1.5:1 “Extent of Exposure” the column label for treatments A and R will be supplemented with the substance name “Diclofenac”. A new characteristic “Administered Gel (g) on Day 7” summarizing the tube weight differences on Day 7 will be added. The summary statistics for “Overall Study” column will not be displayed.

In Listing 16.2.3:1 “Protocol Deviations” the columns “Study Day of Deviation”, “Period”, and “Time Point of Deviation” will be changed for clarification to “Period”, “Study Day Related to Start of Period”, and “Scheduled Time Point”, respectively.

2.2 Clarification and Additional PK Parameters

The SAP defines $C_{\max, ss}$ as the maximum observed concentration at steady state (Day 7) and $t_{\max, ss}$ as the time corresponding to occurrence of $C_{\max, ss}$ at steady state. As this drug was administered BID PK parameters need to be calculated during the dosing interval τ (0-12 h, on Day 7).

The following PK parameters will be derived for the dose interval 0-12 hours on Day 7 (Table 1):

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Table 1: PK parameters for dose interval 0-12 on Day 7

Primary PK parameters	Normalized by weight of administered gel	Normalized by weight of administered gel Without extreme value [1]
AUC _{0-τ, ss} [2]	AUC _{0-τ, ss, norm by gel}	AUC _{0-τ, ss, norm by gel}
C _{max, ss}	C _{max, ss, norm by gel}	C _{max, ss, norm by gel}
t _{max, ss}	-	-

[1]: Calculated only for subject 008 Period 1 Day 7; [2]: Already defined in Final SAP 1.0; -: Parameter will not be calculated

The PK parameters will be listed in Listing 16.2.6:1 and Listing 16.2.6:2 and summarized in Table 15.6.3:1 and Table 15.6.3:2. Original and weight normalized parameters will be sorted in listings and summary tables directly in turn.

2.3 Additional Analyses

During the conduct of the study, a range of actual tube weight differences of 1 g to 5.1 g was observed in contrast to a planned weight of administered gel of 2 g. In order to investigate a possible bias on the study results it was decided to add analyses (Table 2): These will be performed for the primary PK endpoints (AUC_{0-τ, ss} and C_{max, ss}) normalized by the weight of the administered gel on Day 7. Only the weight of Day 7 is used because steady state can be assumed. The analysis will also be done for the extreme value rectified PK parameters.

Please note that normalization by the actual administered dose is not intended. The diclofenac content is different in the investigated products (Diclofenac 2% versus 2.32% topical gel) and the ratio of administered doses can only be maintained by normalizing by the weight of the administered gel.

The final SAP Section 6.3.12.2 “Sensitivity Analysis” will be amended by an extra sensitivity analysis of the main analysis. There will be no changes to the structure/format of the tables, figures and listings based on this change.

Same statistical model and SAS code as per relative bioavailability will be used for additional analyses.

2.4 Supportive and Secondary Analyses

The analysis of the primary PK parameters, with and without extreme value and normalized by weight of administered gel, will also be added to the statistical analyses shown in Table 2. Primary PK endpoints in plasma will be calculated for diclofenac and capsaicin, however, the secondary analysis is not applicable for capsaicin. The statistical analyses will be added to the shells indicated in the following Table 2.


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Table 2: Overview of analyses of PK parameters on Day 7

PK Parameters	Main Analysis Fixed Effects	Sensitivity Analysis Random Effect	Supportive Analysis Race	Secondary Analysis Main Without Extreme Value
Final SAP				
AUC _{0-τ,ss}	x	x	x	x
SAP Addendum				
C _{max, ss}	x	x	x	x
AUC _{0-τ, ss, norm by gel}	x	x	x	x
C _{max, ss, norm by gel}	x	x	x	x
Used shells	T 15.5:1 T 16.1.9.3:1	T 16.1.9.3:2	T 15.5:2 T 16.1.9.3:3	T 15.5:3 T 16.1.9.3:4

Norm by gel: normalized by the weight of administered gel; τ: dosing interval 0-12 hours; ss: steady state; x: requested analysis.

The first two rows in Table 2 display the planned statistical analyses described in the SAP final version 1.0. The clarified PK parameter C_{max, ss} and the additional PK parameters normalized by weight of the administered gel will be added to the statistical analyses as requested above.

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3. TABLES/FIGURES

Table 3: Tables and listings referred in the text

Type	Title number	Title	Population
L	16.2.3:1	Protocol Deviations	Safety Population
L	16.2.5:1	Exposure to Study Drug	Safety Population
L	16.2.6:1	Pharmacokinetic Parameters of Diclofenac	Safety Population
L	16.2.6:2	Pharmacokinetic Parameters of Capsaicin	Safety Population
L	16.2.7:1	Adverse Events	Safety Population
T	15.1.5:1	Extent of Exposure	Safety Population
T	15.5:1	Statistical Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte	Pharmacokinetic Population
T	15.5:2	Supportive Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte and Race	Pharmacokinetic Population
T	15.5:3	Secondary Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte	Pharmacokinetic Population
T	15.5:4	Not applicable output for sensitivity analysis (random effect) can be found in Table 15.5:1 and Table 16.1.9.3:2	
T	15.6.3:1	Summary of Pharmacokinetic Parameters by Product and Analyte	Pharmacokinetic Population
T	15.6.3:2	Summary of Pharmacokinetic Parameters by Product and Analyte and Race	Pharmacokinetic Population
T	16.1.9.3:1	Statistical Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte	Pharmacokinetic Population
T	16.1.9.3:2	Sensitivity Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte	Pharmacokinetic Population
T	16.1.9.3:3	Supportive Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte and Race	Pharmacokinetic Population
T	16.1.9.3:4	Secondary Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte	Pharmacokinetic Population

L: Listing; T: Table

4. LISTINGS

No new listings that are to be produced.

STATISTICAL ANALYSIS PLAN

Sponsor Study Number: 1358.2

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

Version: Final 1.0

Date: 08/Sep/2017

REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 1.0	14/Apr/2017		New Document
Draft 2.0	10/Jul/2017		Detailed revision according to sponsor comments and added tables for
Draft 3.0	24/Jul/2017		Revised PK parameters, BLQ replacement and 2/3 rule
Draft 4.0	22/Aug/2017		Considered AESIs, sort order of CM, revised details for LSM means and supportive analysis, added a table for overall tolerability, rephrased section 'Study Population', revised drug exposure and dose calculation, assessment of relative bioavailability, renamed listings to tables in section 8
Draft 5.0	06/Sep/2017		Added section 6.3.12.4 for a secondary analysis of bioavailability
Final 1.0	08/Sep/2017		

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Declaration

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ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
AESI	AE of special interest
ANOVA	Analysis of Variance
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUC _(0-τ)	AUC over one dosing interval (τ=12 hours)
AUC _(0-τ,ss)	AUC over one dosing interval at steady state (Day 7)
[REDACTED]	[REDACTED]
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
C _{av,ss}	Average concentration at steady state
CI	Confidence interval
C _{last}	Last quantifiable concentration at t _{last}
[REDACTED]	[REDACTED]
C _{max,ss}	Maximum observed concentration at steady state
[REDACTED]	[REDACTED]
CRF	Case report form
CS	Clinically significant
CSP	Clinical Study Protocol
CV	Coefficient of variation
DBP	Diastolic blood pressure
[REDACTED]	[REDACTED]
DRM	Data Review Meeting
ECG	Electrocardiogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
gCV	Geometric CV
gMean	Geometric Mean

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Abbreviation / Acronym	Definition / Expansion
HIV	Human immunodeficiency virus
HR	Heart rate
IMP	Investigational Medicinal Product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculable
NCS	Not clinically significant
NK	Not known
NOA	Not analyzed
NOR	No valid result
PK	Pharmacokinetic
PT	Preferred Term
R	Reference IMP
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SOC	System Organ Class
T	Test IMP
[REDACTED]	[REDACTED]
TEAE	Treatment-emergent adverse event
t_{last}	Time of last quantifiable concentration
TLF	Tables Listings Figures
t_{max}	Time corresponding to occurrence of C_{max}
$t_{max,ss}$	Time corresponding to occurrence of $C_{max,ss}$ at steady state
WHO-DD	World Health Organisation - Drug Dictionary
[REDACTED]	[REDACTED]
%AUC _{ex}	Percentage of AUC _(0-inf) obtained by extrapolation
%PTF	Percentage Peak trough fluctuation

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final CSP, dated, 17/Oct/2016, and revised CSP, dated, 13/Feb/2017 as well as the final Data Management Plan dated 05/Jul/2017. The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

1. STUDY OBJECTIVES

1.1 Primary Objective

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.

1.2 Secondary Objective

[REDACTED]

[REDACTED]

In order to examine potential racial differences in pharmacokinetics (PK), the study population will be stratified 50:50, Caucasian versus Black people. [REDACTED]

[REDACTED]

[REDACTED]

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2. 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.

Details on the medicinal products can be found in Section 8.2 in the CSP. For details relevant for the statistical evaluation please refer to Section 6.3.12 of this SAP.

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 medical 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 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.

3. STUDY POPULATION

Up to 48 eligible subjects (stratified 50:50 Caucasian and Black people) will be enrolled into the study to complete the study with at least 42 evaluable subjects with respect to the planned precision of the estimated relative bioavailabilities.

In order to examine potential racial differences in pharmacokinetics (PK), 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.

Detailed lists of inclusion and exclusion criteria are shown in Sections 7.3.1 and 7.3.2 of the CSP.

4. STATISTICAL BASIS FOR SAMPLE SIZE

The sample size determination is not based on a power calculation, but to assure a precise estimation of relative bioavailability ratios with respect to $AUC_{(0-\tau,ss)}$ 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 (see CSP) regarding $AUC_{(0-\tau,ss)}$ and $C_{max,ss}$ of PENNSAID topical solution and 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 $AUC_{(0-\tau,ss)}$ 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%.

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Table 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 ¹	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

1: T/R: T=Test IMP, R=Reference IMP

5. RANDOMIZATION

A randomization schedule was provided by [REDACTED] Biostatistics. The randomization schedule was 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 [REDACTED].

6. STATISTICAL ANALYSIS CONVENTIONS

6.1 Analysis Variables

6.1.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Medical history (including previous and current medical conditions and medications)
- Alcohol and smoking history
- Age
- Gender

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- Race
- Height, without shoes (cm)
- Body weight (kg)
- Body mass index (BMI) calculated as $[\text{weight}/\text{height}^2]$ (kg/m²)

All medical history will be coded using Version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

6.1.2 Safety Variables

6.1.2.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. More details regarding serious adverse events (SAEs), AEs of special interest, classification of AEs and causal relationship of AEs are defined in the CSP section 12.

All AEs will be coded using version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known).
- Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings.

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6.1.2.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured according to the schedule in section 11:

- **Clinical chemistry:** 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
- **Hematology:** 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
- **Urinalysis:** Glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite and leucocytes
- **Serology:** human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C
- **Drugs of abuse:** amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine (phenylcyclohexalpipерidine), tetrahydrocannabinol, methadone, methamphetamine, tricyclic antidepressants, oxycodone, propoxyphene, cotinine, and alcohol breath test

6.1.2.3 Vital Signs

The following vital signs measurements will be obtained according to the schedule in section 11:

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Pulse rate (bpm)
- Body temperature (oral) [°C]

6.1.2.4 Electrocardiograms

Standard 12-lead ECG will be performed according to the schedule in section 11.

The ECG will be evaluated by the Investigator as ‘Normal’, ‘Abnormal, NCS’ or ‘Abnormal, CS’.

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6.1.2.5 Physical Examination

A full physical examination will be performed according to the schedule in section 11 at screening. At the discretion of the Principal Investigator, a follow-up physical examination will be performed on subjects withdrawn from the study due to an AE. Findings will be listed by body system, including skin evaluation.

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

[REDACTED]

6.1.2.7 Overall Assessment of Tolerability

The patient will assess the overall tolerability of the trial treatment on a 4-point verbal rating scale by answering the question: "How would you rate the overall tolerability of the study medication?" (0 = poor; 1 = fair; 2 = good; 3 = very good). The Investigator should make the corresponding assessment at about the same time as the patient. Assessments should be made independently from each other, i.e.,

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without knowing the other's assessment result when making the assessment. Assessments will be performed according to the schedule in section 11.

6.1.2.8 *Inspection of IMP application sites*

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.

6.1.2.9 *Concomitant Medication*

Concomitant medication will be coded using the World Health Organisation-Drug Dictionary (WHO-DD) (Version WHODDE MAR 2017) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

6.1.3 *Pharmacokinetics Variables*

6.1.3.1 *Pharmacokinetic Parameters*

Unless otherwise stated, derivation of pharmacokinetic (PK) parameters will be the responsibility of Quantitative Clinical Development (QCD), [Redacted] International. The following PK parameters will be determined for diclofenac in plasma following single dose administration:

[Redacted]

[Redacted]	[Redacted]
[Redacted]	[Redacted]
[Redacted]	[Redacted]

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The following pharmacokinetic (PK) parameters will be calculated for Diclofenac in plasma following multiple dose administration:

Table 4 PK Parameters after Multiple Dose Administration for Diclofenac

Parameter	Definition
[REDACTED]	[REDACTED]
$C_{max,ss}$	[1] Maximum observed concentration at steady state (Day 7)
$t_{max,ss}$	[2] Time corresponding to occurrence of $C_{max,ss}$ at steady state
[REDACTED]	[REDACTED]
$AUC_{(0-\tau,ss)}$	[1] AUC over one dosing interval at steady state (Day 7)
[REDACTED]	[REDACTED]
$C_{av,ss}$	[2] Average concentration at steady state (Day 7)
%PTF	[2] Percentage Peak trough fluctuation

[1] primary endpoints; [2] secondary endpoints

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

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6.1.3.2 Pharmacokinetic Parameter Calculation Methods

Diclofenac [REDACTED] PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin (WNL) Professional (Version 6.3) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- Any subjects with missing concentration data will be included in the PK analysis set provided that at least $C_{max,ss}$ and $AUC_{(0-\tau,ss)}$ can be reliably calculated.
- For subjects with pre-morning-dose plasma concentrations on Day 1 in each treatment period, the subject's data may be included without any adjustments in PK parameter derivation for that period, if the pre-dose concentration is $\leq 5\%$ of the individual's maximum observed plasma concentration (C_{max}). If the pre-dose value is $> 5\%$ of C_{max} , the subject's data will be excluded from all bioavailability evaluations.
- For first dose, Day1, parameters, all below the lower limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeros. Thereafter BLQ values between evaluable concentrations will be substituted by missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.
- For dosing Days 5 to 7, BLQ values pre-dose, in the absorption phase, and between evaluable concentrations will be substituted by missing, before the calculation of the PK variables. Terminal BLQ values will be disregarded.

PK parameters will be estimated according to the following guidelines:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

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[REDACTED]

Guidelines for multiple dose, Day 7

- $C_{max,ss}$ at steady state will be obtained directly from the concentration-time data.

[REDACTED]

- $t_{max,ss}$ time at which $C_{max,ss}$ occurs at steady state.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- AUC is calculated as follows:

- The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.

[REDACTED]

[REDACTED]

- $AUC_{(0-\tau),ss}$ Area under the concentration-time curve over the dosing interval.

- $C_{av,ss}$ Average steady-state concentration calculated as $AUC_{(0-\tau),ss}/\tau$.

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The following PK parameters will also be derived using SAS (version 9.3 or higher).

- PTF Peak trough fluctuation calculated as $100\% * (C_{\max,ss} - C_{\text{pre},ss}) / C_{\text{av},ss}$.

6.2 Analysis Populations

6.2.1 Safety Population

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

6.2.2 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 ($AUC_{(0-\tau,ss)}$ [$\tau = 12$ 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 have impact on the analysis of the PK data.

Additionally, samples with relevant time deviations may be excluded from statistical analysis.

Any data excluded will be discussed in the CSR.

6.3 Statistical Analysis Methods

6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as population characteristics will be listed and described using summary statistics. Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All listings will include repeated and unscheduled measurements.

The following rules will apply to any repeated measurements:

- If the repeated measurement occurs prior to the first dose of study drug then the last obtained value of any repeated measurement will be used in the descriptive statistics.
- If the repeated measurement occurs after the first dose of study drug then the original value of any repeated measurements will be used in the descriptive statistics.

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All descriptive statistics will be presented by treatment for measurements obtained during each treatment period. The baseline for all measurements (where applicable) will be the last pre-dose measurement within each period. Descriptive statistics for all data obtained at Screening and follow-up will be presented separately.

If a log-transformation of data is required the natural logarithm will be taken unless otherwise stated.

6.3.2 Rounding and Decimal Places

- The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of diclofenac and capsaicin (data permitting) PK concentration data:
 - The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to five significant digits)
 - The mean, SD, geometric mean and median will be tabulated to one more significant digit compared to the source data.
 - Minimum and maximum values will be tabulated to the same precision as the source data.
 - Geometric CV% will be presented to two decimal places.
- The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of diclofenac and capsaicin (data permitting) PK parameters:
 - Individual PK parameters will be presented to three significant digits, with the exception of [REDACTED] which will be presented to two decimal places. In addition, parameters directly derived from source data (e.g. C_{max}) shall be reported with the same precision as the source data
 - The mean, gMean, median and SD values will be reported to one more significant digit than the source data, except for CV% which will be presented to two decimal places. For [REDACTED] the median, minimum and maximum will be presented to two decimal places

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- Geometric least squares means from the statistical analysis will be presented to three significant digits
- Estimates and confidence intervals in the form of percentages will be presented to two decimal places

6.3.3 Statistical Significance Level

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated. All CI will be two-sided 90% Confidence intervals.

6.3.4 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS[®]) Version 9.3 or later [2]. The PK analysis will be performed using WinNonlin Professional Software Version 6.3 or later [3].

6.3.5 Missing Data

There will be no imputation of missing data.

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. For handling of BLQ PK concentrations in non-compartmental analysis see section 6.1.3.2. For handling of BLQ PK concentrations in listings and summaries see section 6.3.11.1.

6.3.6 Interim Analysis

Not applicable.

6.3.7 Protocol Deviations

All protocol deviations will be recorded by the Investigator and will be listed by subject and will include a description of the deviation, the data/time of the deviation (if available), study day of the deviation, time point (if applicable). Protocol deviations will be reported based on the safety population.

All protocol deviations will be discussed between [REDACTED] (physician, Data Manager, Biostatistician and PK Scientist/Analyst) and also the Sponsor during the Data Review Meeting (DRM) before

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database lock. Protocol deviations will be classified as major or minor. Exclusion/inclusion of subjects from analysis populations (see 6.2) based on the deviations will be decided upon at the DRM. The classifications and further characteristics will be specified in a separate document (Protocol Deviation Specifications dated 20 Jul 2017), the protocol deviations specification. The main categories for protocol deviations that will be considered are described in the following table.

Table 6 Protocol Deviations Categories

Code	Category
INEX	Subject did not meet the inclusion/exclusion criteria
CM	Subject received prohibited concomitant medications
DOSE	Subject did not receive the planned dose
TIME	Deviations from scheduled procedure time outside of the window allowance
PROCEDURE	Procedures not performed due to error or subject availability
PROCESS	Deviations regarding sample processing
ICF	Use of the incorrect ICF, ICF incorrect, etc.
OTHER	Any deviation that does not fit into one of the categories listed above

The window allowance document (WAD, version 1, 28Mar2017) will stipulate the tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

6.3.8 Demographic Data

All demographic data will be presented using 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).

6.3.9 Concomitant Medication

Prior and concomitant medication will be coded and listed using the safety population. Concomitant medication is a medication that is taken after 2 weeks before the first administration of the IMP is taken and during the study up to the follow-up visit or the subject withdraws from the study. Prior medications will be listed first for all subjects followed by all concomitant medications.

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6.3.10 Exposure to the Investigational Medicinal Product

Exposure to the IMPs will be shown in a listing, including weight of the tube before and after dosing. The dose will be calculated from the difference in tube weights (g) and the percentage content of diclofenac and capsaicin:

$$\text{Dose}_{\text{diclofenac}} [\text{mg}] = (\text{Tube weight difference} * 1000 [\text{mg}]) * 0.02 \quad \text{for test products 1(A) and 2(B)}$$

$$\text{Dose}_{\text{diclofenac}} [\text{mg}] = (\text{Tube weight difference} * 1000 [\text{mg}]) * 0.0232 \quad \text{for reference product C}$$

$$\text{Dose}_{\text{capsaicin}} [\text{mg}] = (\text{Tube weight difference} * 1000 [\text{mg}]) * 0.00075 \quad \text{for test product 2(B)}$$

Afternoon tube weights not available in the database will be imputed by using the previous and the subsequent weights.

A table will summarize per subject dosing variables: the number of actual doses, the dose of diclofenac and capsaicin per administration, the cumulative dose, the number of days as well as the total dose over all subjects by treatment and overall in the study.

6.3.11 Pharmacokinetic Concentrations and Variables

The statistical analysis of the PK data will be based on the PK population. Listings will be based on the safety population.

Diclofenac and capsaicin (data permitting) pharmacokinetic concentration data will be listed by subject including actual sampling times relative to dosing. Plasma concentrations will be summarized by treatment and time point. Values that are BLQ will not be substituted to zero for the calculation of descriptive statistics of concentration by time point. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV), gMean, gCV (calculated as: $\text{gCV} = \text{SQRT}(e^{s^2} - 1) * 100$; where s is the standard deviation of the log-transformed values and e is the exponential function), median, minimum and maximum values. The same summary statistics will be provided by treatment and treatment and race.

Individual plasma concentration for diclofenac and capsaicin versus actual times will be plotted by treatment for each analyte in linear and semi-logarithmic scale. Mean and gMean plasma concentrations versus nominal times will also be presented in linear and semi-logarithmic scale. All treatments will be overlaid on the same plot, and each analyte will receive separate plots.

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Descriptive statistics of concentrations at a specific nominal time point will be calculated if at least 2/3 of the individuals have numerical concentration values. The total number of samples that were drawn at the specific time point include BLQ (below the lower limit of quantification), NOR (no valid result) and NOA (not analyzed). No descriptive statistics will be determined when less than 2/3 individual PK parameters are available.

PK parameters that could not be reliably estimated and statistical parameters (except the number of observations n) that fail due to the 2/3 rule will be displayed as NC “not calculable” in the listings or summary tables

Diclofenac and capsaicin (data permitting) pharmacokinetic parameters will be listed by subject and summarized by treatment and by treatment and race. Descriptive statistics (n, arithmetic mean, gMean, median, gCV, CV, SD, minimum, 10th percentile [P10], 25th percentile [Q1], 75th percentile [Q3], 90th percentile [P90] and maximum) for calculated PK parameters will be provided per treatment. For t_{max}, only median, minimum and maximum values will be presented.

6.3.11.1 Handling of Values Below the Limit of Quantification (BLQ) in Concentration Summaries, Listings and Graphical Presentations

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:

All concentrations below the limit of quantification (BLQ), NOR, NOA or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis. Values that are BLQ, NOR or NOA will not be substituted for the calculation of descriptive statistics of concentration by time point.

Graphical presentation:

For graphs of arithmetic means all calculations will follow the rules for summaries. All BLQ values after the last quantifiable concentration will be excluded from individual linear/linear and log/linear graphs.

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6.3.12 Assessment of Relative Bioavailability

6.3.12.1 Main Analysis

Relative bioavailability will be estimated for the primary diclofenac PK parameters (Table 4) by the ratios of the gMeans (test/reference [T/R]) for AUC(0- τ ,ss) and C_{max,ss} at steady state (refer to 6.1.3 and [4]). 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. 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. These methods are in line with the EMA guideline [4].

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). 90% CIs for the difference will be calculated based on the residual error from ANOVA. Least squares means will be tabulated with 90% CIs. The differences between the test and reference product and the CIs will be back-transformed to the original scale.

The following comparisons will apply:

- Test Product 2 (B) vs Reference (C)
 - i.e. B: Diclofenac + Capsaicin versus C: Diclofenac sodium topical gel (Voltarol®)
- Test Product 2 (B) vs Test Product 1 (A)
 - i.e. B: Diclofenac + Capsaicin versus A: Diclofenac sodium

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

The treatment group labels that will be used in the TLFs are defined in a separate document (Table, Listing and Figure Shells).

The following SAS code will form the basis of the analysis:

```
PROC MIXED;  
    CLASS treatment_code period sequence subject;  
    MODEL var=treatment_code sequence period subject(sequence);  
    /*where var= log transformed primary PK endpoints*/  
    LSMEANS treatment_code / PDIF CL ALPHA=0.1;  
    ODS OUTPUT LSMEANS = ls_means;  
QUIT;
```

Before the data will be analyzed the fixed effect treatments will be coded; Test product 2 (B)=T and Reference (C)=R. For the comparison Test Product 2 (B) vs Test product 1 (A) the coding will be Test product 2 (B)=T and Test Product 1 (A)=R. This coding is needed to obtain the correct order for nominator and denominator i.e. T/R in the procedure output of SAS.

[REDACTED]

[REDACTED]

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

6.3.13 Safety Analysis

The analysis of the safety variables will be based on the safety population.

6.3.13.1 Adverse Events

An AE will be assigned to the treatment period in which the AE starts (principle of treatment emergent AE (TEAE)).

The following listings will be produced:

- All pre-treatment AEs and TEAEs.
- Withdrawals due to AEs (if applicable).
- SAEs (if applicable).
- SAEs leading to death (if applicable)
- AESIs

The following information will be included in the listings: AE number, reported term, System Organ Class (SOC), Preferred Term (PT), start and end date/time, intensity, causality, action taken, outcome, classified as serious and treatment emergence.

Numbers of TEAEs will 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 of the causal relationship, the AEs will be grouped into 2 categories, namely “Related” and “Not Related”. For more details see CSP section 12.3.

AEs will be summarized for disclosure on European Union drug regulating authorities Clinical Trials database (EudraCT).

Hepatic Injury

Hepatic injury is an AE of special interest (AESI, CSP section 12.1.3) and was assessed and categorized as AESI during the treatment periods, recorded on the case report form (CRF), and must be

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reported by the Investigator (CSP section 12.4). During the DRM AESI data will be presented and the occurrence of AESIs will be confirmed by the study team. Data Management will capture AE of special interest in SDTM SUPPAE domain, a supportive to the SDTM AE dataset. This enables to include the frequencies of AESI in the overall summary table.

6.3.13.2 Clinical Safety Laboratory Tests (hematology, clinical chemistry and urinalysis)

Laboratory values (hematology, clinical chemistry and urinalysis) will be listed by subject and visit.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS) or repeated (Rep). Clinically significant laboratory values will be recorded by the Investigator as AEs.

Descriptive statistics (for non-categorical data including hematology and clinical chemistry) will be presented by Visit (N, mean, SD, median, minimum, maximum).

Serology, pregnancy test and drugs of abuse results will be listed with other laboratory parameters.

6.3.13.3 Vital Signs

Vital signs data will be listed by subject including changes from baseline. The baseline for the vital signs measurements will be the pre-dose measurement on Day 1 of each period.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and changes from baseline will be presented by visit and treatment.

6.3.13.4 12-Lead Electrocardiogram

All ECG parameters obtained from the ECG measurement will be listed by subject by visit. Descriptive statistics (n, mean, SD, median, minimum, maximum) will be given for absolute values by visit.

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[REDACTED]

6.3.13.6 Overall Tolerability

Overall tolerability scores will be listed by visit and assessor (patient or investigator) and frequency and percentages will be displayed by overall, treatment and visit and by treatment and race.

6.3.13.7 Inspection of IMP Application Site

Visit dates, times and comments from inspection of IMP application site will be listed.

6.3.13.8 Physical Examination

The results of the physical examination will be listed by subject and visit.

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7. REFERENCES

1. EMA/CPMP/EWP/280/96 Corr1, Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, 21 February 2013.
2. SAS[®] Version 9.3 of the SAS System for Personal Computers. Copyright © 2012. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
3. WinNonlin Professional Software Version 6.3. <http://www.pharsight.com>
4. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, Guideline on the investigation of bioequivalence, London, 20 January 2010.

8. CLINICAL STUDY REPORT

Subsections marked with hash (#) do not include outputs because the section is either not applicable or outputs are included in another section.

15.1 TRIAL SUBJECTS

15.1.1 Disposition of subjects

Table 15.1.1: 1 Subject Disposition by Treatment Sequence and Overall (Safety Population)

15.1.2 Definition of analysis sets

Table 15.1.2: 1 Subject analysis sets

15.1.3 Important protocol violations

15.1.4 Demographic data and baseline characteristics - including diagnoses and therapies

Table 15.1.4:1 Demographic Characteristics (Safety Population)

15.1.5 Extent of exposure

Table 15.1.5:1 Extent of Exposure (Safety Population)

15.1.6 Compliance data

Table 15.1.6:1 Compliance Data (Safety Population)

15.2 EFFICACY EVALUATION

15.3 SAFETY EVALUATION

15.3.1 Adverse Events

Table 15.3.1:1 Summary of Treatment-Emergent Adverse Events by Product (Safety Population)

Table 15.3.1:2 Serious Treatment-Emergent Adverse Events by Product, System Organ Class and Preferred Term (Safety Population)

Table 15.3.1:3 Adverse Events by Product, System Organ Class and Preferred Term (Safety Population)

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Table 15.3.1:4	Adverse Events by Product, System Organ Class, Preferred Term and Causality (Safety Population)
Table 15.3.1:5	Adverse Events by Product, System Organ Class, Preferred Term and Intensity (Safety Population)
Table 15.3.1:6	Adverse Events for disclosure on EudraCT by Treatment (Safety Population)
Table 15.3.1:7	Non-Serious Adverse Events for disclosure on EudraCT by Treatment (Safety Population)
Table 15.3.1:8	Serious Adverse Events for disclosure on EudraCT by Treatment (Safety Population)

15.3.2 Clinical Laboratory Evaluation

Table 15.3.2:1	Hematology (Safety Population)
Table 15.3.2:2	Clinical Chemistry (Safety Population)

15.3.3 Vital Signs – Physical Findings and Other Relevant Observations Related to Safety

Table 15.3.3:1	Vital Signs (Safety Population)
Table 15.3.3:2	12-Lead Electrocardiogram (Safety Population)

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

Table 15.3.3:5	Summary of Overall Tolerability (Safety Population)
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15.4 STANDARD SAFETY TABLES

15.4.1 Possible clinically significant abnormal laboratory value listing

Table 15.4.1:1	Abnormal Clinical Chemistry Values (Safety Population)
Table 15.4.1:2	Abnormal Hematology Values (Safety Population)

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15.4.2 Listings of deaths - other serious adverse events - adverse events of special interest and other significant adverse events

Table 15.4.2:1 Serious Adverse Events Leading to Death (Safety Population)

Table 15.4.2:2 Serious Adverse Events (Safety Population)

Table 15.4.2:3 Adverse Events Leading to Discontinuation (Safety Population)

Table 15.4.2: 4 Adverse Events of Special Interest (Safety Population)

15.5 STATISTICAL EVALUATION OF CLINICAL PHARMACOLOGY ENDPOINTS

Table 15.5:1 Statistical Analysis of Primary Pharmacokinetic Endpoints in Plasma by Analyte (Pharmacokinetic Population)

[REDACTED]

15.6 CLINICAL PHARMACOLOGY EVALUATION

15.6.1 Drug concentration-time data

Table 15.6.1:1 Summary of Plasma Concentrations versus Nominal Sampling Times by Product and Analyte (Pharmacokinetic Population)

Table 15.6.1:2 Summary of Plasma Concentrations versus Nominal Sampling Times by Race, Product, and Analyte (Pharmacokinetic Population)

15.6.2 Pharmacokinetic parameters

15.6.3 Overall Summary of Pharmacokinetic parameters

Table 15.6.3:1 Summary of Pharmacokinetic Parameters by Product and Analyte (Pharmacokinetic Population)

Table 15.6.3:2 Summary of Pharmacokinetic Parameters by Product Analyte and Race (Pharmacokinetic Population)

15.6.4 Demographic data #

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15.6.5 Pharmacokinetic Figures

- Figure 15.6.5:1** Plasma Diclofenac Arithmetic Mean Concentrations in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:2** Plasma Diclofenac Arithmetic Mean Concentrations in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:3** Plasma Diclofenac Geometric Mean Concentrations in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:4** Plasma Diclofenac Geometric Mean Concentrations in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:5** Plasma Capsaicin Arithmetic Mean Concentrations in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:6** Plasma Capsaicin Arithmetic Mean Concentrations in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:7** Plasma Capsaicin Geometric Mean Concentrations in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:8** Plasma Capsaicin Geometric Mean Concentrations in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:9** Plasma Diclofenac Arithmetic Mean Concentrations in Linear Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:10** Plasma Diclofenac Arithmetic Mean Concentrations in Semi-logarithmic Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:11** Plasma Diclofenac Geometric Mean Concentrations in Linear Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:12** Plasma Diclofenac Geometric Mean Concentrations in Semi-logarithmic Scale by Race (Pharmacokinetic Population)

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- Figure 15.6.5:13** Plasma Capsaicin Arithmetic Mean Concentrations in Linear Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:14** Plasma Capsaicin Arithmetic Mean Concentrations in Semi-logarithmic Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:15** Plasma Capsaicin Geometric Mean Concentrations in Linear Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:16** Plasma Capsaicin Geometric Mean Concentrations in Semi-logarithmic Scale by Race (Pharmacokinetic Population)
- Figure 15.6.5:17** Individual Plasma Diclofenac Concentrations in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:18** Individual Plasma Diclofenac Concentrations in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:19** Individual Plasma Capsaicin Concentrations in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:20** Individual Plasma Capsaicin Concentrations in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:21** Combined Individual Diclofenac Concentrations by Product in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:22** Combined Individual Diclofenac Concentrations by Product in Semi-logarithmic Scale (Pharmacokinetic Population)
- Figure 15.6.5:23** Combined Individual Capsaicin Concentrations by Product in Linear Scale (Pharmacokinetic Population)
- Figure 15.6.5:24** Combined Individual Capsaicin Concentrations by Product in Semi-logarithmic Scale (Pharmacokinetic Population)

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9. APPENDICES TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

Outputs marked with hash (#) are not applicable to the study.

Appendix 16.1.9.1 Statistical Analysis Plan

Appendix 16.1.9.2 Statistical Analysis – efficacy – safety #

Appendix 16.1.9.3 Statistical Analysis of Clinical Pharmacology

Table 16.1.9.3:1 Statistical Analysis of Primary Pharmacokinetic Parameters of Diclofenac in Plasma (Pharmacokinetic Population)

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Appendix 16.1.9.4 Analytical reports

Appendix 16.1.9.5 Individual log-linear graphs from WinNonlin

10. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CSR

16.2 SUBJECT DATA LISTINGS

16.2.1 Disposition of subjects - discontinued subjects

Listing 16.2.1:1 Subject Disposition (Safety Population)

Listing 16.2.1:2 Failed Inclusion Criteria (Safety Population)

Listing 16.2.1:3 Failed Exclusion Criteria (Safety Population)

16.2.2 Subjects excluded from the efficacy analysis

Listing 16.2.2:1 Assignment to Analysis Populations (Safety Population)

16.2.3 Protocol Deviations

Listing 16.2.3:1 Protocol Deviations (Safety Population)

16.2.4 Demographic data

Listing 16.2.4:1 Subject Demographics (Safety Population)

Listing 16.2.4:2 Medical History (Safety Population)

Listing 16.2.4:3 Alcohol and Tobacco Consumption (Safety Population)

Listing 16.2.4:4 Prior and Concomitant Medication (Safety Population)

16.2.5 Exposure - compliance and - or drug concentration data

Listing 16.2.5:1 Exposure to Study Drug (Safety Population)

Listing 16.2.5:2 Individual Blood Sampling Times and Plasma Concentrations (Safety Population)

16.2.6 Pharmacokinetic Data

Listing 16.2.6:1 Pharmacokinetic Parameters of Plasma Diclofenac

Listing 16.2.6:2 Pharmacokinetic Parameters of Plasma Capsaicin

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16.2.7 Adverse Event listings

Listing 16.2.7:1 Adverse Events (Safety Population)

16.2.8 Listing of individual laboratory measurements by subject and other relevant observations related to safety

16.2.8.1 Clinical laboratory

Listing 16.2.8.1:1 Hematology (Safety Population)

Listing 16.2.8.1:2 Clinical Chemistry (Safety Population)

Listing 16.2.8.1:3 Urinalysis (Safety Population)

Listing 16.2.8.1:4 Other Laboratory Parameter (Safety Population)

16.2.8.2 Other relevant observations related to safety

Listing 16.2.8.2:1 Vital Signs (Safety Population)

Listing 16.2.8.2:2 12-Lead Electrocardiogram (Safety Population)

[REDACTED] [REDACTED]
Listing 16.2.8.2:4 Overall tolerability (Safety Population)

Listing 16.2.8.2:5 Inspection of IMP application site (Safety Population)

Listing 16.2.8.2:6 Physical Examination (Safety Population)

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11. 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													

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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	
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				
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)	

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

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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 of protocol 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 (phenylcyclohexylpiperidine), 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.

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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 of protocol 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 (\pm 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 of the protocol.