Clinical Trial Protocol

	Document Number:	**c03317678-02**
EudraCT No.:	2015-000404-25	
BI Trial No.:	1358.1	
BI Investigational Products:	Diclofenac + Capsaicin	
Title:	A randomized, controlled multi-centre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain	
Brief Title:	Capsaicin/diclofenac gel in acute back pain or neck pain	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Phone: [redacted], Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted], Fax: [redacted]	
Status:	Final Protocol	
Version and Date:	**Version: 2.0**	**Date: 21 Jun 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:			
Name of active ingredient:		**Diclofenac + Capsaicin**	
Protocol date: 09-Dec-2015	**Trial number:** 1358.1		**Revision date:** 21-Jun-2016

Title of trial:	A randomized, controlled multi-centre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain
Coordinating Investigator:	[redacted] Phone: [redacted], Fax: [redacted]
Trial site(s):	Multi-centre trial, conducted in 2 countries
Clinical phase:	III
Objective(s):	To assess the efficacy and tolerability of a topical formulation gel of the combination of diclofenac and capsaicin in comparison to gels with diclofenac alone, capsaicin alone, and placebo for the treatment of acute back pain or neck pain. The primary objective of this trial is to demonstrate superior efficacy of a formulation containing a combination of 2% diclofenac and 0.075% capsaicin over placebo and over formulations containing 2% diclofenac alone and 0.075% capsaicin alone for the treatment of acute back or neck pain. A secondary objective is to assess the safety and tolerability of the combination of diclofenac and capsaicin in comparison to gels with diclofenac alone, capsaicin alone.
Methodology:	Randomized, double-blind, placebo- and active-controlled, multi-centre 4-arm parallel group study, conducted in 2 countries
No. of patients:	
total entered:	Approximately 800 to achieve 700 patients eligible for the assessment of the primary endpoint
each treatment:	Diclofenac and capsaicin: 240 Diclofenac: 240 Capsaicin: 240 Placebo: 80
Diagnosis :	Acute back pain or neck pain

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Main criteria for inclusion:	Male or female patients ≥ 18 years with current diagnosis of acute back pain or of neck pain. Acute back pain or acute neck pain resulting in pain on movement (POM) ≥50 mm (VAS 0-100) for at least one POM procedure out of 5 standardized procedures. Sensitivity to algometric pressure on the painful trigger point ≤ 25 N/cm²
Test product:	Capsaicin + diclofenac gel
dose:	0.075% Capsaicin, 2% diclofenac sodium, 2 g formulation (40 mg diclofenac sodium, 1.5 mg capsaicin) twice daily
mode of administration:	Topical
Comparator product 1:	Capsaicin gel
dose:	0.075% Capsaicin, 2 g formulation (1.5 mg capsaicin) twice daily
mode of administration:	Topical
Comparator product 2:	Diclofenac gel
dose:	2% Diclofenac sodium, 2 g formulation (40 mg diclofenac) twice daily
mode of administration:	Topical
Comparator product 3:	Placebo gel
dose:	Not applicable, 2 g formulation twice daily
mode of administration:	Topical
Duration of treatment:	Screening and start of treatment at the same visit (Visit 1) 5 day treatment period 2 day follow-up period
Endpoints	Primary endpoint: • Change in POM_{WP} (for the worst procedure, i.e. the procedure leading to maximum pain) between baseline and Day 2 evening, 1 hour after drug application Key secondary endpoints • $POM_{WP}AUC_{72}$ (Area under the curve of POM_{WP} assessed until Day 4 morning, i.e. 72 hours after start of treatment) • $POM_{WP}AUC_{120}$ (Area under the curve of POM_{WP} assessed until Day 6 morning, i.e. 120 hours after start of treatment) Other secondary endpoints: • Number of patients with a decrease in POM_{WP} of at least 30% from baseline on Day 2 evening, 1 hour after drug application

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	• Number of patients with a decrease in POM_{WP} of at least 50% from baseline on Day 2 evening, 1 hour after drug application • Change in POM_{WP} between baseline and the morning of Day 6 • Change in Pressure Algometry (PA) between baseline and Day 2 evening, before drug application • Change in PA between baseline and the morning of Day 6
Safety criteria:	Skin check, incidence of adverse events, physical examination, vital signs, safety laboratory parameters, patient and investigator assessment of tolerability
Statistical methods:	For the primary endpoint • Change in POM_{WP} between baseline and Day 2 evening, 1 hour after drug application and the secondary endpoints • Change in POM_{WP} between baseline and the morning of Day 6 • Change in PA between baseline and Day 2 evening, before drug application • Change in PA between baseline and the morning of Day 6, restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment, time, the stratification factors country and application site (back/neck) as discrete fixed effects, baseline POM_{WP} as a continuous fixed effect, and interaction between time and treatment as well as baseline POM_{WP} and time. The primary treatment comparison will be the contrast between treatments at the endpoint time, respectively. The key-secondary endpoints $POM_{WP}AUC_{72}$ and $POM_{WP}AUC_{120}$ will be analysed using analysis of covariance including treatment, country and application site (back/neck) as fixed effects and the baseline POM_{WP} as a continuous covariate. The number of patients with a decrease in POM_{WP} of at least 30% or 50%, respectively, from baseline until Day 2 evening, 1hour after drug application, will be analysed by a logistic regression model, including the factor treatment and the categorical stratification factors country and application site (back/neck).

FLOW CHART

Visit[K]	**1**			**Hm**	**2**			**3**			**4**			**Hm**	**5**			**Hm**	**Hm**		**6**	**7T Fllw up**
Day	**1**				**2**						**3**				**4**				**5**[D]		**6**[D]	**8**[D]
Time window for visits	**±0**				**±0**			**±0**			**±0**				**±0**						**-1/+2**	**-1/+4**
Approximate day time[B]	**M**			**E**	**M**[C]			**E**[C]			**M**			**E**	**M**			**E**	**M**	**E**	**M**	
Timing rel. to application[H]	**Pre**	**Apl**	**Post**	**Apl**	**Pre**	**Apl**	**Post**	**Pre**	**Apl**	**Post**	**Pre**	**Apl**	**Post**	**Apl**	**Pre**	**Apl**	**Post**	**Apl**	**Apl**	**Apl**		
Patient information and informed consent	X																					
Demographics	X																					
Medical history	X																					
Previous therapies	X																					
Concomitant therapies	X				X			X			X				X						X	X
Vital signs	X																				X	
Physical examination	X																					
Pain On Movement (POM)[L]	X		X[I]				X[I]	X		X[I]			X[I]				X[I]				X	
Pressure Algometry (PA)	X				X			X			X				X						X	
Urine pregnancy test[E]	X																					
Safety laboratory tests	X																				X	
[redacted]	X		X[G]		X		X[N]	X		X[N]	X		X[N]		X		X[N]		X[M]		X	
[redacted]	X			X[F]						X[F]				X[F]				X[F]		X[F]		
Review of in-/exclusion criteria	X																					
Randomization via Interactive Response Technology (IRT)	X																					
Weighing of trial medication/ drug accountability	X																				X	
Dispense of trial drug and gloves; Instructions on use	X																					
Application of trial drug		X		X		X			X			X		X		X		X	X	X		
Dispense rescue medication; Instructions on use			X														X[J]					

Visit[K]	**1**			**Hm**	**2**			**3**			**4**			**Hm**	**5**			**Hm**	**Hm**		**6**	**7T Fllw up**
Day	**1**				**2**			**3**			**4**				**5**[D]						**6**[D]	**8**[D]
Time window for visits	**±0**				**±0**			**±0**			**±0**				**±0**						**-1/+2**	**-1/+4**
Approximate day time[B]	**M**			**E**	**M**[C]			**E**[C]			**M**			**E**	**M**			**E**	**M**	**E**	**M**	
Timing rel. to application[H]	**Pre**	**Apl**	**Post**	**Apl**	**Pre**	**Apl**	**Post**	**Pre**	**Apl**	**Post**	**Pre**	**Apl**	**Post**	**Apl**	**Pre**	**Apl**	**Post**	**Apl**	**Apl**	**Apl**		
Hand-out of patient diary; Instructions on use			X				X			X			X				X					
Assessment of skin reactions			X[N]				X[N]			X[N]			X[N]				X[N]				X	
[redacted]			X[G]				X[G]																
[redacted]				X[F]						X[F]				X[F]				X[F]		X[F]			
[redacted]			X[G]																				
Patient diary: Use of rescue/other medication				Continuously																		
Transfer of patient diary entries to electronic Case Report Form (eCRF)					X			X			X				X						X	
Return of patient diary					X			X			X				X						X	
Overall [redacted] and tolerability assessment by patient and by investigator																					X	
Return of trial drug and rescue medication																					X	
Adverse events			X		X			X			X				X						X	X
Completion of patient participation																					X[A]	X[A]

A Completion of patient participation also needs to be completed if the patient withdraws prematurely following randomization (see Section 3.3.3)

B M = Morning; E = Evening; Morning visits should generally be performed between 7:00 am and 11:00 am.

C Visits 2 and 3 need to be planned so that the evening application of the trial medication can be administered 12 hours (±4 hours) after the morning application.

D Date of Visit 6 has to be agreed based on patient's availability and severity of pain. Standard treatment duration is 5 days (Day 1-5) with Visit 6 on Day 6. Treatment could be shortened to 4 days (with Visit 6 on Day 5) or extended to 6 days (with Visit 6 on Day 7; home procedures indicated in the Flow Chart for Day 5 to be repeated on Day 6) or 7 days (with Visit 6 on Day 8; home procedures indicated in the Flow Chart for Day 5 to be repeated on Day 6 and 7). Visit 7T should be performed at least 2 days and no later than 4 days after Visit 6.

E For women of childbearing potential only

[redacted]

G Parameters to be assessed by the patient 0.5 (±5 min), 1 (±10 min but before POM assessments), 3 (±15 min) and 6 (±15 min) hours after the morning application of the trial drug. Results will be entered into the patient diary.

H Pre = before application; Apl = Application; Post = after application. The application time at each visit is to be documented in the eCRF.

I Assessment 1 hour (±10 min) after application of trial medication

J Optional second dispense of rescue medication

K Hm = Home procedure; Fllw up = Follow up

L All five POM assessments need to be performed at Visit 1 before application. Once POM_{WP} is determined, only POM_{WP} and the other POM procedures related to the same stratum (either back or neck pain) as POM_{WP} need to be performed at subsequent assessments (see Section 5.2.1)

M To be assessed by the patient at home directly before and 1 hour (±10 min) after the morning application of the trial drug

N To be assessed 1 hour (±10 min) after application of the trial drug and before POM assessments

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[redacted]

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine transaminase
[redacted]	[redacted]
ASS	Acetyl salicylic acid
AST	Aspartate transaminase
BI	Boehringer Ingelheim
BP	Blood Pressure
CA	Competent Authority
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBP	Diastolic blood pressure
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
MedDRA	Medical Dictionary for Drug Regulatory Activities
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over The Counter
PA	Pressure Algometry
p.o.	per os (oral)
POM	Pain On Movement
POM_{WP}	Pain On Movement of worst procedure (leading to maximum pain at baseline)
$POM_{WP}AUC_{72}$	Area under the curve of POM_{WP} assessed until Day 4 morning, i.e. 72 hours after start of treatment
$POM_{WP}AUC_{120}$	Area under the curve of POM_{WP} assessed until Day 6 morning, i.e. 120 hours after start of treatment
[redacted]	[redacted]

[redacted]	[redacted]
RDC	Remote Data Capture
REML	Restricted Maximum Likelihood
REP	Residual Effect Period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unsuspected Serious Adverse Events
TCM	Trial Clinical Monitor
TENS	Transcutaneous Electrical Nerve Stimulation
[redacted]	[redacted]
TRPV1	Transient Receptor Potential Vanilloid 1
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
VRS	Visual Response Scale

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Back pain is a very common disorder with a point prevalence of approximately 35% in Germany [P11-08387]. In most cases specific causes cannot be identified (i.e. “unspecific low back pain”). Usually, low back pain is a self-limiting disorder, and approximately 90% of patients experience remission within 6 weeks. Musculoskeletal pain in the back area is worsened through a vicious circle of excessive muscle (force) load inducing pain (by minor muscle injury and local muscle ischaemia) that causes non-physiological posture, which in turn causes further pain.

Neck pain is becoming increasingly common throughout the world. The point prevalence of neck pain ranges from 0.4% to 41.5% (mean: 14.4%); and 1 year prevalence ranges from 4.8% to 79.5% (mean: 25.8%). Prevalence is generally higher in women, higher in high-income countries compared with low- and middle-income countries and higher in urban areas compared with rural areas [R12-4817]. Much neck pain is not attributable to a specific disease or disorder and is labelled as “soft-tissue” rheumatism or muscular/ mechanical/ postural neck pain [R15-2389].

Acute back/ neck pain is often treated with over the counter (OTC) analgesics, such as paracetamol, ibuprofen, or naproxen. Other treatment options are local heat [P11-08754] and hyperaemisation inducing agents [R11-2672]. Local heat and hyperaemisation inducing treatment were shown to augment blood flow and haemoglobin oxygenation in the skin and in the muscles [R11-2636, P11-05079]. Thus, such treatments can be assumed to be beneficial in the treatment of such musculoskeletal conditions.

Remedies against acute back/ neck pain, especially in an OTC environment, are required to reduce back discomfort fast and effectively while being tolerated well.

NSAIDs have been used since decades for the treatment of back and neck pain. A systematic review concluded that NSAIDs are effective for short-term symptomatic relief in patients with acute and chronic low back pain without sciatica. However, effect sizes are small [P08-09510]. In a recent review [P15-04711] topical options for the treatment of back/neck pain has been discussed. In a clinical trial a hyperaemisation inducing agent has been shown to reduce back/neck pain with low incidence of side effects [P11-00252].

Topically applied remedies seem to have a low potential for systemic side effects and interactions with other (including systemic) medications.

1.2 DRUG PROFILE

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 [P13-15601, P08-12601].

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 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 [P13-09858].

Combination rationale

Capsaicin has been shown to act as a penetration enhancer (e.g. for indomethacin [R10-0978], naproxen [R14-1637] 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 actives 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 Investigator's Brochure (IB, [c03404356]) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Diclofenac and capsaicin ointments/gels have been used for decades to treat complaints of the musculoskeletal system. However, no clinical trials have been performed to demonstrate analgesic effects for the combination of diclofenac and capsaicin in treatment of back or neck pain.

The aim of this study is to assess the efficacy and tolerability of diclofenac/capsaicin gel in comparison to diclofenac, capsaicin, and placebo gels for the treatment of acute back or neck pain to obtain market authorizations for this indication.

2.2 TRIAL OBJECTIVES

The objective of this pivotal study is to assess the efficacy and tolerability of a topical formulation gel of the combination of diclofenac and capsaicin in comparison to gels with diclofenac alone, capsaicin alone, and placebo for the treatment of acute back pain or neck pain.

The primary objective of this trial is to demonstrate superior efficacy of a formulation containing a combination of 2% diclofenac and 0.075% capsaicin over placebo and over formulations containing 2% diclofenac alone and 0.075% capsaicin alone for the treatment of acute back or neck pain.

A secondary objective is to assess the safety and tolerability of the combination of diclofenac and capsaicin in comparison to gels with diclofenac alone, capsaicin alone.

2.3 BENEFIT - RISK ASSESSMENT

Topical application forms containing either diclofenac or capsaicin have been in clinical use for a long time and the available safety and tolerability data show that both are well tolerated and safe. Data from post marketing surveillance show that most of the reported unwanted effects of capsaicin gels are in line with the mechanism of action, e.g. skin burning sensation, erythema and pruritus for capsaicin gels. The most common side effects of diclofenac are application site reactions, including erythema, itching, burning sensation and rash. A combination of both safety profiles is expected for the combination of diclofenac and capsaicin.

Overall, the long term clinical experience with diclofenac or capsaicin gels and the aforementioned safety profiles of both present a favourable benefit risk assessment which would support proceeding with this trial.

Although very rare in topical administration, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely

detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also Section 5.3.6.1.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is a prospective, randomised, double-blind, parallel group, multi-centre trial to show superiority in terms of reduction of Pain on Movement (POM) of a topical combination containing diclofenac 2% and capsaicin 0.075% compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% when applied twice daily over 4 to 7 days to patients with acute back pain or neck pain. A total of approximately 800 patients will be randomised to the treatment groups diclofenac + capsaicin, diclofenac, capsaicin and placebo in a 3:3:3:1 ratio in order to achieve 700 patients eligible for the assessment of the primary endpoint.

After a screening evaluation (Visit 1), eligible patients will be randomised into the double-blind treatment phase of the trial. After administration of the first treatment, the patients will administer the second application of the trial medication in the evening at home. They will return to the trial site for four more visits (Visits 2 to 5) in the morning and in the evening of the following day (Day 2) and in the morning of Days 3 and 4 and thereby be dosed while at the site. Evening applications on Day 3 and Day 4 will be administered by the patients at home. Thereafter, the treatment will be administered at home for one more day (Day 5). The patients will then return to the trial site for final assessments (Visit 6) in the morning of Day 6. The trial participation will be concluded by a telephone call (Visit 7T) for follow-up on adverse events (AEs) on Day 8.

Depending on the severity of a patient's condition and on a patient's availability, the treatment-period at home (Day 5) could be skipped or extended by one or two days. Visit 6 should then be performed on the day immediately following to that shortened or extended period.

The interval between two applications of the trial medication should be 12 hours. This interval could be shortened or extended by 4 hours as long as no more and no less than two applications are administered on each treatment day.

Patients who discontinue the application of the trial medication prematurely, should be encouraged to contact the site immediately so that Visits 6 and 7T could be performed on the day immediately after discontinuation.

The study will be conducted at approximately 20 study centres in Germany and Russia. The trial will end with completion of the last follow-up call (Visit 7T) with the last patient.
For a graphical representation of the trial, see Figure 3.1: 1.

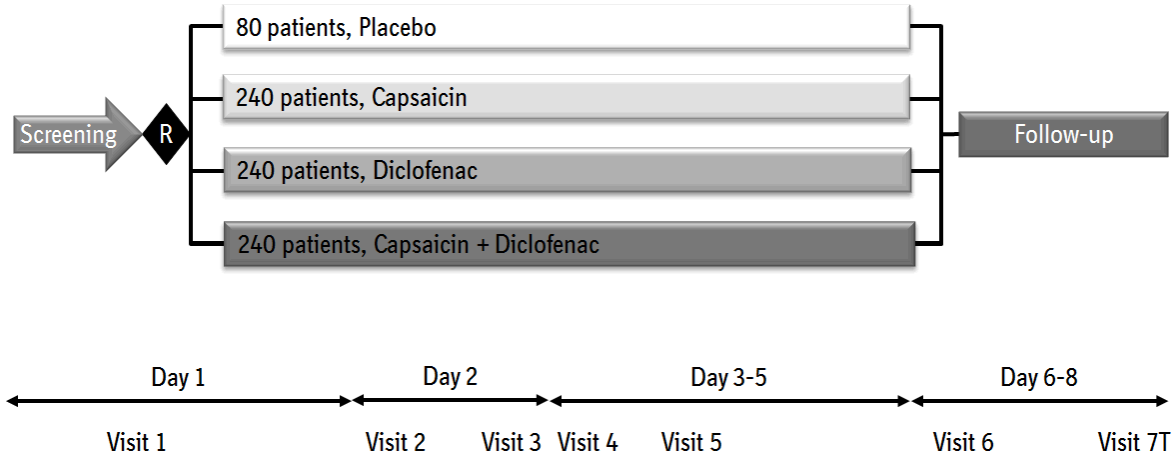


Figure 3.1: 1 Trial design, R = randomisation

3.1.1 Administrative structure of the trial

Boehringer Ingelheim (BI), the sponsor of this trial, has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

The sponsor will designate appropriately qualified personnel to advice on trial-related topics.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF and the Clinical Trial Master File (CTMF).

A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in CTMF.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in the ISF.

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

The study design of this trial is based on the Guideline on Clinical Development of Fixed Combination Medicinal Products of the EMA's Committee for Medicinal Products for Human Use (CHMP) [R09-2704]. The design is suited to assess the effect of a gel containing diclofenac and capsaicin on acute back or neck pain compared with gels containing the individual components, diclofenac or capsaicin, or placebo. Comparison with the individual components is necessary to confirm a clinically meaningful effect of the combination in terms of pain relief. Comparison with placebo is necessary to assess the overall relative effect of the combination of diclofenac and capsaicin.

Assessment of pain at rest provides important information on patients comfort during treatment [P08-09626]. However, for measurement of pain at rest patients tend to move into a relieving posture which limits the value of the measurement to reflect patient's restriction in performing daily activities. Other than at rest, functional limitations become obvious during movement. Functional improvement can be detected by standardized movements [R14-1467]. Thus, POM was selected as the primary variable for assessment of pain relief. For back and neck pain standardized movements have been established [R14-1467, R12-4427].

For the assessment of the primary endpoint, POM_{WP} 1 hour after the evening application on Day 2 will be compared to POM_{WP} at baseline. Typically a treatment effect of topical treatments can be observed after 1 to 3 days. The chosen time frame for assessment of the primary endpoint allows sufficient time for the trial treatment to become effective. On the other hand it is sufficiently short to avoid diminishing differences by the self-limiting properties of acute back or neck pain. Similar time frames were chosen in comparable clinical trials [R14-1467, R12-4427].

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients with acute back or neck pain will be screened. It is assumed that approximately 800 patients will need to be randomized at around 20 trial sites to achieve 700 patients who are evaluable with regard to the primary endpoint.

It is expected that around 40 patients will be randomised at each trial site. If enrolment is delayed, additional sites may be recruited. Permission to randomise more than 80 patients per site must be obtained from the Trial Clinical Monitor (TCM) at BI. This will only be allowed after a careful review of the enrolment status and of the site.

Screening of patients for this trial is competitive across all countries and sites within the trial, i.e. screening for the trial will stop at all sites when it is anticipated that a sufficient number of patients have been screened to yield the desired number of patients randomised to trial treatment. Investigators will be notified when sufficient patients have been screened and when screening is complete, and will not be allowed to recruit additional patients for the study.

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

3.3.1 Main diagnosis for trial entry

Only patients with acute neck or back pain will be screened for suitability for the study.

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

3.3.2 Inclusion criteria

1. Signed and dated written informed consent at Visit 1 in accordance with Good Clinical Practice (GCP) and local legislation.

2. Male or female patients ≥18 years with current diagnosis of acute back pain or of neck pain for at least 24 hours, but less than 21 days.

3. Acute back pain or acute neck pain resulting in pain on movement (POM) ≥ 50 mm (VAS 0-100) for at least one POM procedure out of 5 standardized procedures.

   The POM measurement with the highest pain response will determine if the patient has back or neck pain (see Section 5.2.1 for further details).

4. Sensitivity to algometric pressure on the painful trigger point ≤ 25 N/cm² (see Section 5.2.2).

5. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

   *Women of childbearing potential are defined as:
   Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

   Women not of childbearing potential are defined as:
   Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

3.3.3 Exclusion criteria

1. History of 3 or more episodes of back or neck pain in the last 6 months excluding the current episode

2. Surgery due to back or neck pain or rehabilitation due to back or neck pain in the last 12 months.

3. Back or neck pain that is attributable to any specific identifiable cause (e.g. disc prolapse, spondylolisthesis, osteomalacia, inflammatory arthritis, metabolic, neurological diseases or tumour).

4. Trauma or strains of the back or neck muscles within the last 3 months.

5. Prior use within the last 3 days before Visit 1 or concomitant use of any anti-inflammatory drugs, heparinoids, muscle relaxants or analgesics (including but not limited to short-acting glucocorticoids, non-steroidal anti-inflammatory drugs [NSAIDs], herbal preparations).

   Long-acting glucocorticoids must have been discontinued 10 days before study entry.

   Spinal injections should have been discontinued in due time (investigator's judgement) before patient enrolment to allow complete wash-out of the active ingredient based on investigator's judgment.

   Exceptions: Acetyl salicylic acid (ASS) up to 100 mg/day for cardiovascular therapy, antidepressants or antipsychotics on stable dose for at least 2 weeks prior to Visit 1. Use of inhaled glucocorticoids (e.g. for asthma or chronic obstructive pulmonary disease) is acceptable.

6. Non-pharmacological treatment (physiotherapy, heat treatment (e.g. heat patch, hot water bottle), or massage, acupuncture, transcutaneous electrical nerve stimulation [TENS]) or locally applied pharmacological product to the back or neck area 24 hours prior study entry and during the study period.

7. Known severe hepatocellular insufficiency, severe renal insufficiency or Gilbert's syndrome (Morbus Meulengracht)

8. Any other medical condition that would interfere with efficacy and safety assessments based on investigator's judgement or any on-going clinical condition that would jeopardize patient's or site personnel's safety or study compliance based on investigator judgement.

9. Known intolerance or hypersensitivity to the active ingredients or any excipient(s).

10. Patients in whom attacks of asthma, bronchospasm, rhinitis or urticaria were precipitated by the intake of ASS or other NSAIDs

11. Irritated skin (based on investigator's judgement), skin wounds, eczema or open injuries at application site (the trial medication should only be applied to intact, non-diseased skin)

12. Negative experience in the past with heat treatments for muscle complaints (e.g. heat pads, hyperaemisations inducing topical creams, gels, ointments, patches)

13. Patient not able to understand and comply with trial requirements based on investigators judgement

14. Alcohol or drug abuse within 3 months prior to Visit 1 that would interfere with trial participation based on investigator's opinion.

15. Participation in a clinical trial within the previous 30 days before enrolment in the trial, participation in this study before or simultaneous participation in another clinical trial.

16. Women who are pregnant, nursing, or who plan to become pregnant while in the trial (see also Section 4.2.2.3).

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from trial treatment if:

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product (see Section 3.3.3) or other trial medication. See Section 4.2.2 for further details.
- The patient can no longer be treated with trial medication or rescue medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)

If a patient becomes pregnant during the trial the study medication will be stopped, the patient will be discontinued from the trial and the patient will be followed up until birth or otherwise termination of the pregnancy.

A patient can be discontinued after discussion between Sponsor and Investigator if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at study assessments).

Patients who drop out during the screening prior to randomisation will be considered screening failures. They will be recorded as screening failures in the eCRF and no further follow-up is required. The data will be included in the trial database and will be reported.

Patients who discontinue or withdraw from the study after randomisation will be considered as "early discontinuations" and the reason for this premature discontinuation must be recorded in the eCRF. The Investigator must inform the sponsor within 24 hours ~~via IRT~~ (see Section 4.1) about any premature discontinuation of a subject. The data will be included in the trial database and will be reported. Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up (Visits 6 and 7T) as outlined in the Flow Chart and Section 6.2.3.

For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The study medication will be provided by BI.

4.1.1 Identity of BI investigational product and comparator products

The characteristics of the test and comparator products are as shown in Tables 4.1.1: 1, 4.1.1: 2, 4.1.1: 3 and 4.1.1: 4.

Table 4.1.1: 1 Test product: capsaicin + diclofenac gel

Substance:	Capsaicin Diclofenac sodium
Pharmaceutical formulation:	Gel
Source:	C.P.M. ContractPharma GmbH & Co. KG Arzneimittelherstellung und Verpackung
Unit strength:	0.075% capsaicin 2% diclofenac sodium 50g tubes
Posology	The single dose of the combination product (diclofenac sodium 2% and capsaicin 0.075%) is 2 g formulation (40 mg diclofenac sodium, 1.5 mg capsaicin) to be applied on the skin. A twice daily application is proposed resulting in maximum daily dose of 4 g formulation (80 mg diclofenac sodium, 3.0 mg capsaicin).
Route of administration:	Topical

Table 4.1.1: 2 Comparator product 1: diclofenac gel

Substance:	Diclofenac sodium
Pharmaceutical formulation:	Gel
Source:	C.P.M. ContractPharma GmbH & Co. KG Arzneimittelherstellung und Verpackung
Unit strength:	2% diclofenac sodium 50g tube
Posology	The single dose of the diclofenac gel (diclofenac sodium 2%) is 2 g formulation (40 mg diclofenac sodium) to be applied on the skin. A twice daily application is proposed resulting in maximum daily dose of 4 g formulation (80 mg diclofenac sodium).
Route of administration:	Topical

Table 4.1.1: 3 Comparator product 2: capsaicin gel

Substance:	Capsaicin
Pharmaceutical formulation:	Gel
Source:	C.P.M. ContractPharma GmbH & Co. KG Arzneimittelherstellung und Verpackung
Unit strength:	0.075% capsaicin 50g tube
Posology	The single dose of the capsaicin gel (capsaicin 0.075%) is 2 g formulation (1.5 mg capsaicin) to be applied on the skin. A twice daily application is proposed resulting in maximum daily dose of 4 g formulation (3.0 mg capsaicin).
Route of administration:	Topical

Table 4.1.1: 4 Comparator product 3: placebo gel

Substance:	N/A
Pharmaceutical formulation:	Gel
Source:	C.P.M. ContractPharma GmbH & Co. KG Arzneimittelherstellung und Verpackung
Unit strength:	Not applicable
Posology	The single dose of the placebo gel is 2 g formulation to be applied on the skin. A twice daily application is proposed resulting in maximum daily dose of 4 g formulation.
Route of administration:	Topical

4.1.2 Method of assigning patients to treatment groups

When a patient is qualified for randomisation, treatment assignment will be by means of a third-party randomisation system at Visit 1. This will involve the use of IRT, which will take into consideration the relevant stratification factors (for further details see Section 7.6). To facilitate the use of IRT, the Investigator will receive all necessary instructions and/or documents for using the IRT.

Patients will be randomly assigned, in a 3:3:3:1 ratio, to either:

(i) diclofenac and capsaicin
(ii) diclofenac
(iii) capsaicin
(iv) placebo

For further details refer to Section 7.6. Entry into the application site stratum “back pain” will be capped as soon as 60% of the total trial population have been allocated to this stratum. Vice versa, the application site stratum “neck pain” will be capped as soon as 60% of the total trial population have been allocated to this stratum.

Patient assignment to the treatment groups will be determined by a computer generated random sequence. Access to the randomisation code will be controlled and documented. For further details please refer to Sections 4.1.5.1 and 4.1.5.2.

A single trial medication kit corresponding to the assigned medication number should be given to the patient and the number of the kit that was/were dispensed will be entered in the eCRF. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.3 Selection of doses in the trial

Both, capsaicin and diclofenac are contained as single active compounds in marketed products. The doses of the active ingredients in this trial correspond to standard doses of such products. For reference see e.g. the Summaries of Product Characteristics (SmPCs) of ABC Lokale Schmerz-Therapie Wärme-Creme 750 µg/g and Voltarol® 12 Hour Emulgel®.

4.1.4 Drug assignment and administration of doses for each patient

Patients should be equipped with disposable gloves and instructed to wear them whenever applying the trial medication.

The gel will be applied to the region on the patient's back or neck where he/she feels the pain. If possible, the application should always be done by the patient himself/herself. An area of approximately 20 cm x 20 cm (corresponding to approximately two hand sizes) will be treated, covering the region on the patient's back or neck where he/she feels the most pronounced pain as identified by POM assessment (Section 5.2). A gel drop of approximately the size of a hazelnut will applied to the patient's gloved hand and quickly massaged into the POM_{WP} area. Following applications should be administered approximately 12 hours (±4 hours) from each other but not more and not less than twice daily up until the evening before Visit 6. The minimum treatment duration is 4 days, the maximum is 7 days.

If an application of the trial medication is missed, that application should be skipped and the next application should be taken as scheduled.

Patients should be instructed not to apply their trial medication in the morning before Visits 2 and in the evening before Visit 3 as the medication will be applied at the site. They should also be instructed that the medication is to be applied lastly in the evening before Visit 6. The actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock. The randomization code will be kept secret by Clinical Trial Support up to database lock.

The incidence of unblinding due to a warming effect of nonivamide can be considered very low, since a previous study investigating nonivamide [U13-2315-01] revealed a marked proportion of patients, who perceived some warming although not treated with nonivamide, and as well, revealed a marked proportion of patients, who perceived no warming although treated with nonivamide. Blinding will further be supported by applying the study medication with gloves.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate Case Report Form (CRF) page along with the date and the initials of the person who broke the code.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

Each medication kit will consist of one tube of 50 g gel in an outer carton. For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

The trial medication must be kept in its tightly closed original packaging under the recommended storage conditions indicated on the label. A temperature log must be maintained by the Investigator/Pharmacist/investigational drug storage manager to make certain that the medication is stored at the correct temperature. If storage conditions are found to be outside the specified range, the process outlined in the ISF should be followed.

Trial medication must be stored securely at the study sites, out of reach of children and be protected from moisture and direct sunlight, e.g. in a locked cupboard or at a Pharmacy. It may only be dispensed to trial patients fulfilling the inclusion and exclusion criteria by authorised study personnel as documented in the ISF. Receipt, usage and return of the trial medication must also be documented on the respective forms in the ISF.

All unused medication including all packaging, empty or filled, must be either returned to the Sponsor, or, following written authorisation from the Sponsor, may be destroyed at site. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

The Investigator/ pharmacist/ investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / Independent IEC Committee (IEC),
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority (CA),

- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator (if applicable)

The Investigator/ pharmacist/ investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

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

4.1.8.1 Patient treatment compliance

Records will be kept regarding when and how much of each study medication is dispensed to, and used by each individual patient in the study. This will be done by measuring the weight of the medication tubes (with cap, without the outer packaging) prior to dispense at Visit 1 and upon return by the patient at Visit 6. Both values will be recorded in the CRF. Appropriate scales should be used which display the tube weight with at least 1 decimal place (0.1 g). Tube weights should always be determined with the same device.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Paracetamol tablets (500 mg tablets) will serve as rescue medication as it is recommended as first line treatment in guidelines for the treatment of acute back or neck pain, e.g. the German National care guideline: low back pain [P11-08387]. Following the first application of study medication, patients may use paracetamol (one to two tablets of 500 mg per os (p.o.), up to twice daily; i.e. up to 4 tablets/ 2 g per day at maximum) for treating intolerable back or neck pain. Similar rescue concept were used in comparable clinical trials [R14-1467, R15-2151, R12-4428, R15-2150].

The patient must always record the number of tablets and the day and time a dose is taken in his/her diary.

Patients should be strongly encouraged not to take any rescue medication until Visit 3. Patients are advised to seek medical advice if the pain persists or the patient's condition worsens, and/or if the rescue medication is used up.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following concomitant treatments are not permitted during the trial for the trial indication or other indications as they would interfere with the efficacy assessments in this trial: any anti-inflammatory drugs, heparinoids, muscle relaxants or analgesics (including but not limited to long- and short-acting glucocorticoids, non-steroidal anti-inflammatory drugs [NSAIDs], herbal preparations), spinal injections, muscle relaxants, other topical pharmaceutical products at the back or neck area, antidepressants, antipsychotics, and other treatments for back or neck pain, such as physiotherapy, heat treatment (e.g. heat patch, hot water bottle), or massage, acupuncture, transcutaneous electrical nerve stimulation (TENS).

Exceptions are paracetamol as rescue medication, ASS up to 100 mg/day for cardiovascular therapy, antidepressants or antipsychotics on stable dose as from at least 2 weeks before randomisation are permitted.

4.2.2.2 Restrictions on diet and life style

No restrictions on diet are required. Patients should be informed that during treatment they might experience an increased sensitivity towards heat (e.g. during sun exposure, hot showers etc).

4.2.2.3 Restrictions regarding women of childbearing potential

Topical application of diclofenac (Voltarol® 12 Hour Emulgel®) is contraindicated in the 3rd trimester of pregnancy. A strict indication is required in 1st and 2nd trimester. The safety of capsaicin has not been established in either humans or animals. Women of child-bearing potential must therefore continue to practice a highly effective method of birth control (in accordance with the trial inclusion criteria Section 3.3.2) throughout the duration of the study.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary endpoint is the change in pain on movement (POM) between baseline and Day 2 evening, 1 hour after drug application (Visit 3) with regard to the POM of the procedure which gave the highest score at baseline ("POM of worst procedure", POM_{WP}).

Throughout the protocol the term 'baseline' refers to the assessment in the morning before the first drug application on Day 1.

POM is assessed by the patient on one standardized movement by using a Visual Analogue Scale (VAS) ranging from 0 mm = 'no pain' to 100 mm = 'worst pain possible for this condition'.

5.1.2 Key Secondary Endpoints

- $POM_{WP}AUC_{72}$. AUC will be calculated as area under the curve from zero to 72 hours using the trapezoidal rule divided by the observation time. Application date/times will be the basis for the calculation of respective time intervals.

- $POM_{WP}AUC_{120}$. AUC will be calculated as area under the curve from zero to 120 hours using the trapezoidal rule divided by the observation time. Application date/times will be the basis for the calculation of respective time intervals.

5.1.3 Other Secondary Endpoints

- Number of patients with a decrease in POM_{WP} of at least 30% from baseline on Day 2 evening, 1 hour after drug application (Visit 3)
- Number of patients with a decrease in POM_{WP} of at least 50% from baseline on Day 2 evening, 1 hour after drug application (Visit 3)
- Change in POM_{WP} between baseline and the morning of Day 6 (Visit 6)
- Change in Pressure Algometry (PA) between baseline and Day 2 evening, before drug application (Visit 3)
- Change in PA between baseline and the morning of Day 6 (Visit 6)

[redacted]

[redacted]

5.2 ASSESSMENT OF EFFICACY

5.2.1 Pain On Movement

POM will be assessed by the patient at the performance of one standardized, muscle group specific movement and is measured by a Visual Analogue Scale (VAS) ranging from 0 mm = 'no pain' to 100 mm = 'worst pain possible for this condition'. The change in POM will be calculated as POM at baseline subtracted by the POM at a given time point.

POM assessment must always be supported by the same adequately trained person (according to trial-specific certification process) in an individual patient.

Baseline POM will be assessed using the following standard procedures [R12-4427, R14-1467]:

1. Musculus trapezius (upper part)

   Position: the patient sits on a chair and the examiner stands behind him/her and fixes his/her shoulders. The examiner determines which shoulder the patient pulled his/her head towards (Figure 5.2.1: 1).

   Test: The patient pulls his/her head sideways towards the left or the right shoulder as appropriate without lifting up the shoulder at the same time.

Figure 5.2.1: 1

2. Musculus erector spinae (upper part)

   Position: The patient sits on a chair and the examiner stands behind him/her and fixes his/her shoulders with his hands. The patient's back leans against the back of the chair (Figure 5.2.1: 2).

   Test: The patient tries to place his/her chin onto the chest without lifting up the shoulders at the same time and without losing contact with the back of the chair.

Figure 5.2.1: 2

3. Musculus levator scapulae

   Position: The patient sits on a chair with hanging arms and the examiner stands behind and fixes his/her shoulders with his hands (Figure 5.2.1: 3).

   Test: The patient tries to lift the arms over the side upwards against the gentle resistance of the examiner's hands.

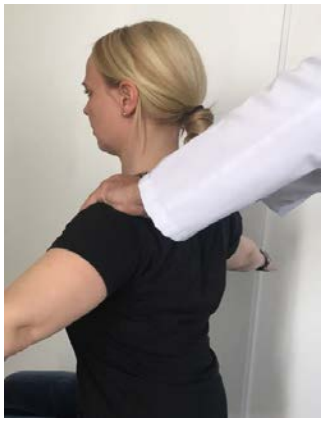


Figure 5.2.1: 3

4. Musculus erector spinae (lower part)

   Position: The patient lies with his/her front on a examination bed. The hips do not lie on the examination bed. With his/her hands, the patient holds on to the right and left edges of the examination bed (Figure 5.2.1: 4).

   Test: The patient bends his/her legs to reach a square angle, lifts his/her thighs up towards the horizontal line.

Figure 5.2.1: 4

5. Musculus rectus abdominis

   Position: The patient lies on the back, legs extended, arms crossed behind his/her head. Both legs are stretched and lifted up to reach a right angle to the surface the patient is lying on. The spine has full contact to the surface (Figure 5.2.1: 5).

   Test: The patient slowly lowers down the stretched legs to the surface.

Figure 5.2.1: 5

Procedures 1-3 indicate neck pain, procedures 4-5 indicate back pain.

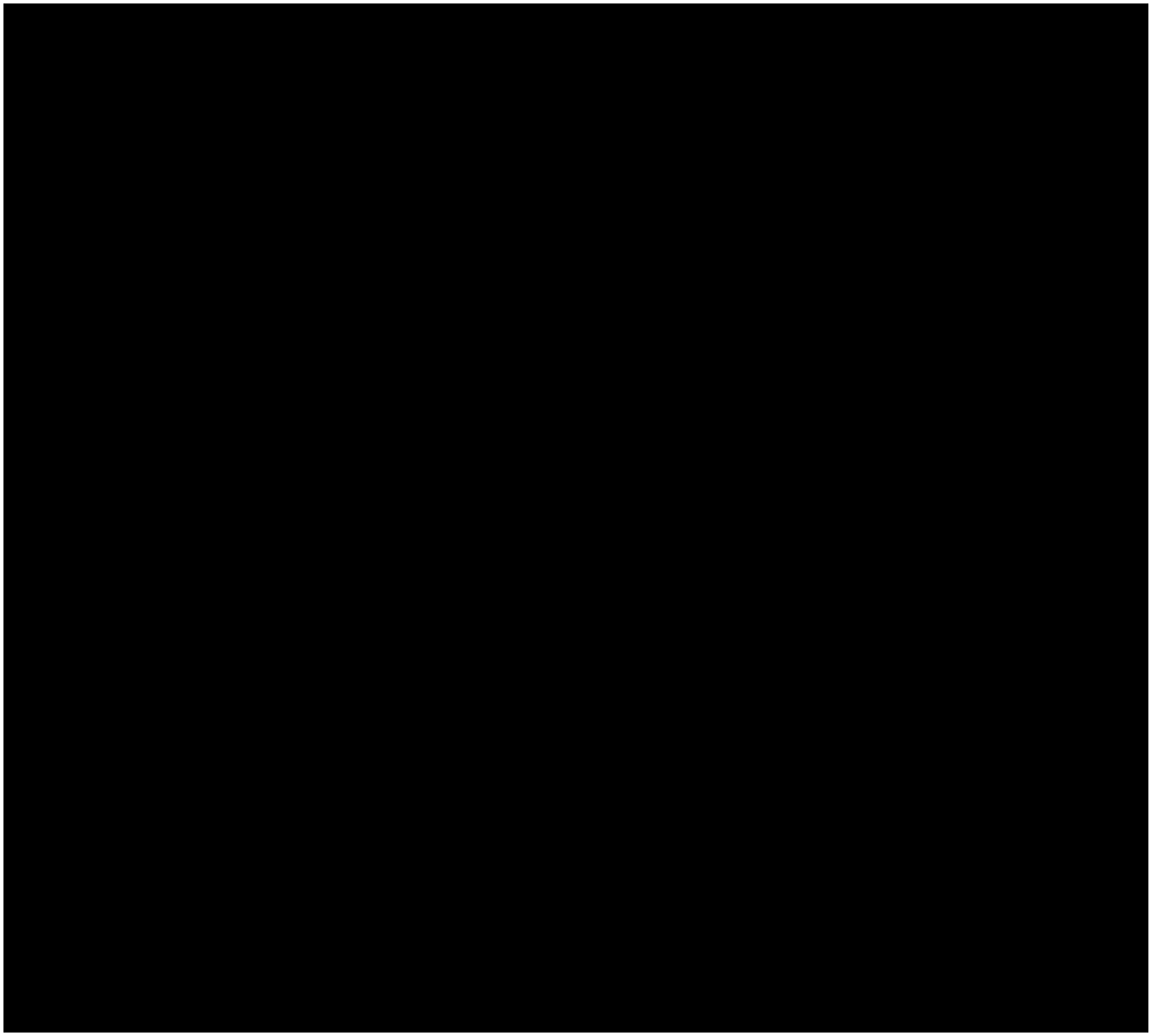
Before randomization, the patients will be provided at the site with 5 separate paper forms each with one horizontal 0-100 mm VAS each. For each procedure performed, the patient will draw a vertical line on the VAS, respectively. The form will collected after each assessment, so that the patient will not see his previous POM assessment. The same ruler should be used for reading the POM value, i.e. by measuring the distance between the 0 mm mark on the VAS and the patient's mark. Assessment forms will be stored with the patient file, results will be entered into the CRF.

The procedure which results in highest POM at baseline and all other procedures related to the same stratum (i.e. all other procedures indicating either neck or back pain, respectively) will be repeated for an individual patient after the first application of trial medication at the time points indicated in the Flow Chart. If two or more procedures give the same highest POM, the patient should be asked which of the procedures giving highest POMs he/she

considers most unpleasant. This specific procedure and all other procedures related to the same stratum should then be reapplied in the course of the patient's trial participation.

5.2.2 Pressure algometry

Pressure algometry (PA) is determined by the investigator at time points indicated in the Flow Chart as the pressure value (N/cm^2) at a defined trigger point which is located in the area of POM_{WP}. The measurement is performed by using a Somedic Algometer (Somedic AB, Sweden) or an equivalent calibrated and certified device. The pain reaction is determined by placing the algometer on the trigger point, i.e. an area of 1 cm² for which the patient indicates most painful tenderness. The pressure is constantly increased until the patient asks not to increase the pressure anymore. Upon this pain reaction, the corresponding pressure value will be documented in the CRF. The trigger point should be marked with a ball pen so that the assessment could always be done at the same position.



5.3 ASSESSMENT OF SAFETY

5.3.1 Assessment of skin reactions

Skin reactions at the application site will be examined and graded approximately 1 hour after each application of the study medication at the site. This assessment will be done by using the numerical Dermal Response Score (DRS) outline in Table 5.3.1: 1 which is based on the DRS described in the "Guideline on the pharmacokinetic and clinical evaluation 4 of modified release dosage forms" (EMA/CPMP/EWP/280/96 Corr1 [R15-1313]).

Clinically relevant dermal reactions should be documented as an AE at investigator's discretion.

Table 5.3.1: 1 Dermal Response Score for assessment of skin reactions

Dermal Response Score	
Score	Score definition
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible
3	Minimal edema or minimal papular response
4	Erythema and papules
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Based on the Dermal Response Score, skin reactions will be categorised as positive for scores ≥3 and negative for scores <3.

5.3.2 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. without knowing the other's assessment result when making the assessment.

5.3.3 Physical examination

A physical examination will be performed by the Investigator or designated site-personnel at the time point indicated in the Flow Chart. Documentation of, and findings from the physical examination, must be part of the source documents available at the site.

5.3.4 Vital Signs

Systolic and diastolic blood pressure (SBP, DBP) as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position at time points indicated in the Flow Chart. The BP measurements should always be performed before drawing blood for lab samples on the non-dominant arm and preferably by the same person and with the same device.

BP measurements should be recorded in the eCRF to the nearest 1 mmHg.

5.3.5 Safety laboratory parameters

A total amount of 11 ml of blood will be taken per patient during the course of the trial for assessment of the laboratory parameters listed in Table 5.3.5: 1. This amount might be exceeded if unscheduled (additional) monitoring is warranted (e.g. in case of suspected DILI).

The laboratory tests will be performed at a central laboratory. Details on collection, labelling, handling, storage and shipping of samples will be provided in a laboratory instruction manual.

Table 5.3.5: 1 Safety laboratory tests

Haematology • Haematocrit • Haemoglobin • Red blood cells (RBC)/erythrocytes • White blood cells (WBC)/leukocytes • Platelet count/thrombocytes • Differential automatic (relative and absolute count):   ○ neutrophils, eosinophils, basophils, monocytes, lymphocytes
Clinical chemistry • Sodium • Potassium • Creatinine • Total Bilirubin • AST (SGOT) • ALT(SGPT) • Alkaline Phosphatase • Gamma GT • Uric Acid • Lipase

Pregnancy testing (urine) will be performed in female patients at time points indicated in the Flow Chart. Further testings might be performed if deemed necessary by the investigator.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

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

Serious adverse event

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

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

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

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be

considered to be "serious" even though they may not have met the criteria of an SAE as given above.
The latest list of "Always Serious AEs" can be found in the RDC system. These events should always be reported as SAEs as described above

Adverse events of special interest (AESIs)

The term AESI 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 timeframe that applies to SAE, see Section 5.3.7.

The following are considered as AESIs:

Hepatic injury

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

- an elevation of AST and/or ALT >3 fold 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 lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided via the RDC-system.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

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

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

Causal relationship of AEs

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

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

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

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

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

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

5.3.7 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate eCRF by the Investigator (see also Figure 5.3.7: 1):

From signing the informed consent onwards through the Residual Effect period (REP), all AEs (serious and non-serious), and AESIs must be reported. However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits including

telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs.

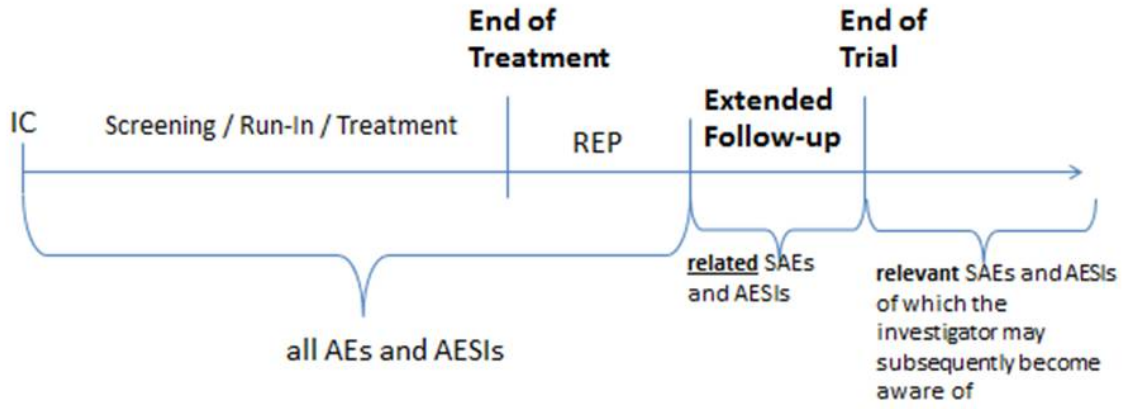


Figure 5.3.7: 1 Graphical depiction of the requirements for AE collection

The REP is defined as 48 hours after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

After the last per protocol contact the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the Investigator.

AE reporting to sponsor and timelines

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

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

Information required

For each AE, the Investigator should provide the information requested on the appropriate

CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drugs and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG (if done outside the trial, not part of the trial assessments), physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

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

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

5.4 APPROPRIATENESS OF MEASUREMENTS

The efficacy tests, instruments and scales used in this trial are widely used and considered reliable, accurate, and relevant in trials for the indication of pain relief.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This trial consists of 6 clinical visits. For the follow-up contact (Visit 7T) the investigator will contact the patient by phone.

If a Visit 2-5 is missed, it should not be re-scheduled. However subsequent visits should follow the original visit schedule. If Visit 6 or Visit 7T is missed, this visit should be re-scheduled to the closest opportunity.

All trial visits except for Visit 3 should take place in the morning, i.e. ideally be started and completed between 7:00 a.m. and 11:00 a.m. Patients must adhere to the visit schedule as specified in the Flow Chart. Visits 2 (Day 2 morning) and 3 (Day 2 evening) need to be scheduled such that the trial medication could be applied according to the required dosing interval of 12 hours (± 4 hours).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The study procedures which are to be performed at each visit are listed in the Flow Chart. Assessments of efficacy and safety are explained in Section 5.2 and 5.3. Assessment of POM, PA and vital signs should preferably be done by the same qualified person for a given patient throughout the study period. This person has to be adequately trained regarding POM and PA and training documentation has to be filed in the ISF.

Additional details regarding visit procedures are provided below.

6.2.1 Screening

Screening will be done during the first part of Visit 1. If a patient's eligibility is confirmed, trial treatment will be initiated. A patient's informed consent has to be obtained prior to the first trial procedures. Following the informed consent process the patient will undergo screening assessments.

It is recommended to perform study procedures in the order as listed in the Flow Chart (column "Pre"). All procedures which are necessary to assess the eligibility of a patient must be performed before randomization. A final assessment of all in- and exclusion criteria should be the last step before making the randomization call in the IRT system.

Documentation of medical history and previous therapies should be restricted to those conditions which are relevant with regard to trial indication and the assessment of the in- and exclusion criteria (see Section 3.3).

All concomitant pharmaceutical and non-pharmaceutical therapies and the corresponding baseline conditions should be documented in the CRF. Other baseline conditions should be

documented if relevant with regard to trial indication and the assessment of the in- and exclusion criteria.

6.2.2 Treatment period

At Visit 1 (Day 1, morning), 2 (Day 2, morning), 3 (Day 2, evening), 4 (Day 3, morning) and 5 (Day 4, morning) the trial medication should be applied at the site and, if possible, by the patient himself/herself. At Visit 1, all procedures indicated in the "Pre" column of the Flow Chart should be performed before the first application of the trial medication. Procedures indicated in the "Post" column should be performed afterwards at time points as indicated.

The trial medication should be weighed, dispensed and applied after randomization without delay. The application times of trial medication will be recorded at the site in the eCRF, where application is performed at the site.

The patient should be instructed

- always to wear gloves when applying the trial medication
- to perform home assessments (warming score, mobility score, time to perceptible/ meaningful pain relieve) at time points indicated in the Flow Chart
- to refrain from using rescue medication before Visit 3 if possible. If this turns out not to be possible, another supply of rescue medication might be dispensed at visit 5
- to record intake of rescue medication (date and number of tablets) in the patient's diary
- to apply the trial medication every 12 (± 4) hours
- to record the time of last application of the trial medication (evening before Visit 6) in the patient's diary
- to return their patient's diary at visit 2, visit 3, visit 4, visit 5 and visit 6
- to return all unused trial and rescue medication and packaging at Visit 6

6.2.3 Follow Up Period and Trial Completion

All study procedures according to the Flow Chart should be performed.

Patients who want to discontinue the trial treatment prematurely should be asked to have Visit 6 in the morning after the last application of the trial medication and to have a Visit 7T at least 48 hours after that last application.

Patients who at the end of their trial participation still require treatment for the trial indication should be treated according to local standard of care.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomized, double-blind, placebo- and active-controlled, multi-country, multi-centre 4-arm parallel group study to investigate efficacy and tolerability of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days (-1/+2 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain.

The patients will be randomised via IRT in blocks to the treatment groups diclofenac + capsaicin, diclofenac, capsaicin and placebo in a 3:3:3:1 ratio. Treatment allocation will be stratified by country and the application site (back or neck) of the study drug; the application site is classified after the POM assessments on a 0-100 mm VAS, following the 5 standard procedures, before application at Visit 1 as that site, where the worst pain is identified, and the corresponding POM is then denoted as POM_{WP}. Post-dose POM_{WP} and POM assessments for the other procedures within the corresponding stratum (back or neck) will be captured each with the same scale and the same standard procedure, respectively. For further details of POM assessments see Section 5.2.1.

Based upon these design considerations, the trial will be analysed using general linear models which will include terms for treatment, country (Germany or Russia), application site (back or neck) and the baseline POM_{WP} as continuous covariate.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary objective of this trial is to demonstrate efficacy of the combination 2% diclofenac + 0.075% capsaicin when compared to both single components (2% diclofenac and 0.075% capsaicin) and placebo for the treatment of acute back or neck pain. This will be primarily evaluated by comparing the change in POM_{WP} between baseline (before application at Visit 1) and Visit 3 (Day 2 evening, 1 hour after application) of the combination treatment against the treatment with the single components and placebo, using two-sided tests and a 0.05 level of significance. To this purpose the following statements are hypothesised:

Null hypothesis:
There is no difference between patients treated with the combination diclofenac + capsaicin and the patients treated with diclofenac or capsaicin alone or placebo.

Alternative hypothesis:
There is a difference between patients treated with the combination diclofenac + capsaicin and the patients treated with diclofenac, patients treated with capsaicin alone and patients treated with placebo.

The set of hypotheses can be written as:

H_0: $H_{0,1}$: $\mu_{diclo+caps} = \mu_{diclo}$ or $H_{0,2}$: $\mu_{diclo+caps} = \mu_{caps}$ or $H_{0,3}$: $\mu_{diclo+caps} = \mu_{placebo}$

versus

H_1: $H_{1,1}$: $\mu_{diclo+caps} \neq \mu_{diclo}$ and $H_{1,2}$: $\mu_{diclo+caps} \neq \mu_{caps}$ and $H_{1,3}$: $\mu_{diclo+caps} \neq \mu_{placebo}$

where, $\mu_{diclo+caps}$, μ_{diclo} , μ_{caps} and $\mu_{placebo}$ is the adjusted (for country and application site effect, and baseline POM_{WP}) mean change in POM_{WP} between baseline (before application at Visit 1) and Visit 3 (Day 2 evening, 1 hour after application) for patients treated with the combination diclofenac + capsaicin, diclofenac, capsaicin or placebo, respectively.

Since all partial hypotheses $H_{0,1}$, $H_{0,2}$ and $H_{0,3}$ are to be rejected in order to reject the null hypothesis H_0, no adjustment for multiplicity issues will be made and thus all statistical testing will be performed using a two-sided, alpha = 0.05 level of significance.

The key secondary endpoints as outlined in Section 5.1.2 will be analysed hierarchically ($POM_{WP}AUC_{72}$ first) in a confirmatory way only, if statistical significance was achieved for the primary endpoint. Therefore, no alpha-adjustment for multiple endpoint testing will be applied.

All other secondary endpoints as outlined in Section 5.1.3 will be considered as supportive only.

7.3 PLANNED ANALYSES

Three analysis datasets will be defined for the purpose of summarizing and analysing the trial data.

Treated set (TS): All randomised patients who used at least one dose of study medication will be included in the treated set. Patients having received the wrong treatment will be analysed within the planned (randomised) treatment group in the efficacy analysis and within the actual treatment group in the safety analysis.

Full analysis set (FAS): All patients included in the treated set, which provide a baseline value before application for POM_{WP} at Visit 1 and at least one POM_{WP} value during the assessment times Visit 1 (Day 1 morning, 1 hour after application), Visit 2 (Day 2, morning, 1 hour after application, Visit 3 (Day 2 evening, before application), Visit 3 (Day 2 evening, 1 hour after application), will constitute the full analysis set.

[redacted]

[redacted]

7.3.1 Primary endpoint analyses

The primary endpoint 'Change in POM_{WP} between baseline (before application at Visit 1) and Visit 3 (Day 2 evening, 1 hour after application)' will be analysed utilising a restricted maximum likelihood (REML) based repeated measures approach, using all available longitudinal POM_{WP} observations at the assessment times T1 = Visit 1 (Day 1 morning, 1 hour after application), T3 = Visit 2 (Day 2, morning, 1 hour after application, T4 = Visit 3 (Day 2 evening, before application) and T5 = Visit 3 (Day 2 evening, 1 hour after application). The statistical model will be applied to the analysis of change from baseline (T0 = Visit 1 morning, before application) in POM_{WP} at times T1, T3, T4 and T5. The statistical model will include the fixed, categorical effects of treatment, country, application site (back/neck), time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline POM_{WP} and baseline-by-time interaction. The definition of baseline POM_{WP} is given in Section 7.1.
An unstructured covariance structure will be used to model the within-patient errors. In case this analysis fails to converge, other covariance structures to be employed will include Compound Symmetry, Autoregressive Model, AR (1) and Spatial Covariance, with the covariance structure converging to the best fit, as determined by Akaike's information criterion, to be used for purposes of comparing treatment effects. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom [R11-1488].

Differences between the treatment group effects (diclofenac/capsaicin - diclofenac, diclofenac/capsaicin - capsaicin, diclofenac/capsaicin - placebo) with regard to the change in POM_{WP} between T0 and T5, calculated as 'POM_{WP} at time T0 - POM_{WP} at time T5' (see Section 5.1) will be estimated by reference to the adjusted least square means and the corresponding 95% confidence intervals (CI). All statistical testing will be performed using a two-sided, alpha = 0.05 level of significance.

The primary analysis will be based on the full analysis set (FAS) as defined in Section 7.3.

In addition to the primary analysis, a separate analysis will be performed to test the heterogeneity of the strata 'application site' and 'country', respectively. In these models the two interaction terms treatment-by-stratum-by- time and stratum-by-time will be added to the primary model, respectively.

[redacted]

[redacted]

7.3.2 Secondary endpoint analyses

The key secondary and other secondary endpoints will be analysed with the treated set as defined for efficacy analysis in Section 7.3.

The key secondary endpoints of $POM_{WP}AUC_{72}$ and $POM_{WP}AUC_{120}$ will be analysed using an analysis of covariance (ANCOVA) including treatment, country and application site (back/neck) as fixed effects and the baseline POM_{WP} as a continuous covariate. Treatment differences will be estimated by reference to the adjusted least square means and the corresponding 95% confidence intervals. The statistical testing will be performed using a two-sided, alpha = 0.05 level of significance.

The number of patients with a decrease in POM_{WP} of at least 30% from baseline until Day 2 evening, 1 hour after drug application, will be analysed by a logistic regression model, adjusting for the categorical covariates country and application site (back/neck). The likelihood-ratio test will be used to test for differences between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing all treatments to the treatment of diclofenac/capsaicin as the reference treatment.

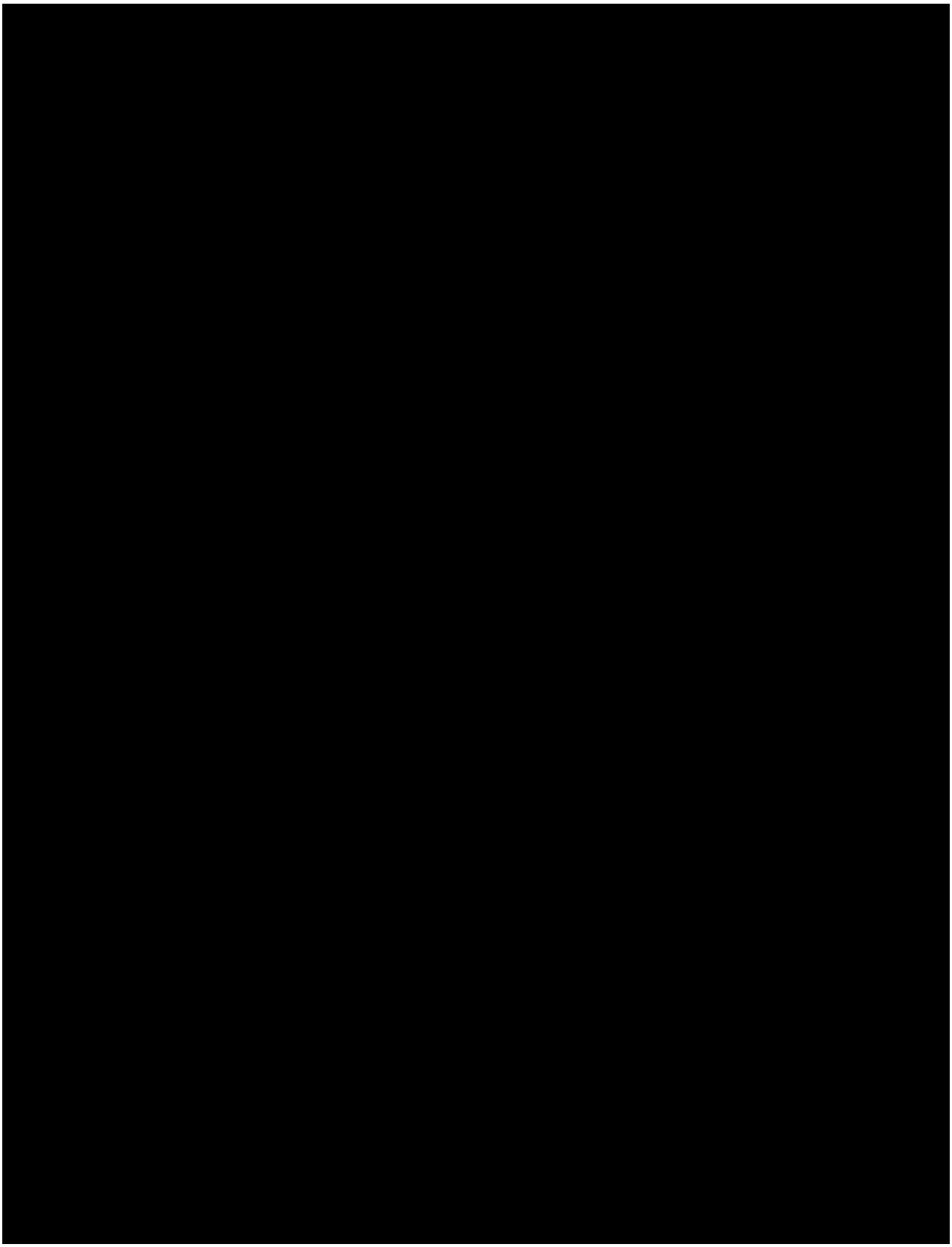
The number of patients with a decrease in POM_{WP} of at least 50% from baseline until Day 2 evening, 1h after drug application, will be analysed correspondingly.

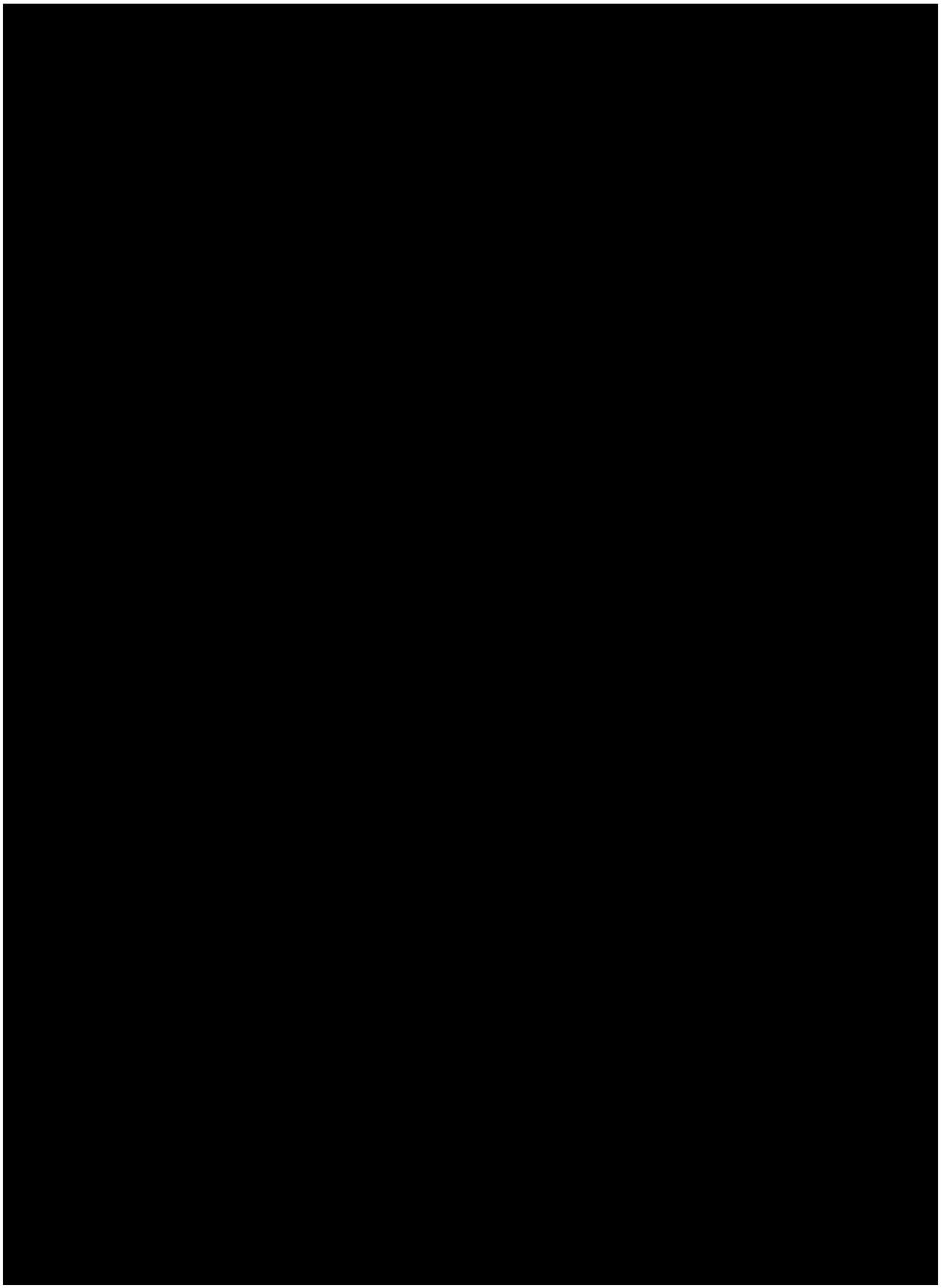
The change in POM_{WP} between baseline and the morning of Day 6 will be analysed analogously to the primary endpoint. The statistical model will be applied to the analysis of change from baseline (T0 = Visit 1 morning, before application) in POM_{WP} at times T1, T3, T4, T5 and - additionally at times T7 (=Visit 4 = Day 3 morning, 1 hour after application), T9 (= Visit 5 = Day 4 morning, 1 hour after application) and T12 (= Visit 6 = morning of Day 6).

The change in PA between baseline and Day 2 evening, before drug application (Visit 3) will be analysed analogously to the primary endpoint using all available longitudinal PA observations at the assessment times T2 = Visit 2 (Day 2 morning, before application) and T4 = Visit 3 (Day 2, evening, before application). The statistical model will be applied to the analysis of change from baseline (T0 = Visit 1 morning, before application) in PA at times T2 and T4.

The change in PA between baseline and the morning of Day 6 will be analysed analogously to the primary endpoint. The statistical model will be applied to the analysis of change from

baseline (T0 = Visit 1 morning, before application) in PA at times T2, T4, T6, T8 and - additionally - T12 (= Visit 6 = morning of Day 6).





7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 48 hours after the last application of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Safety analyses will be done by the actual treatment as defined for safety analysis in Section 7.3.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as a period of 2 days (48 hours) after the last application of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

The final overall patient / investigator assessment of tolerability will be analysed analogously to [redacted]

The assessment of skin reactions will be analysed descriptively.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

Every effort should be made to collect the complete data at the planned time points for this trial.

For the analyses utilising a likelihood-based repeated measures model as described in Section 7.3, no imputation of missing values will be performed.

Missing entries for the assessment of efficacy will be assigned the least favourable category if missing was the result of discontinuation due to lack of efficacy. Missing entries for the assessment of tolerability will be assigned the least favourable category if missing was the result of discontinuation due to drug-related adverse events.

Missing patient assessments of efficacy or tolerability resulting from early discontinuation that was clearly unconnected to treatment will be not imputed.

7.6 RANDOMISATION

Patients will be randomized in blocks to double-blind treatment arms diclofenac + capsaicin, diclofenac, capsaicin and placebo in a ratio 3:3:3:1. The randomization allocation will be stratified by country (Russia, Germany) and application site (back/neck). At least 40% of the randomised total population are aimed to be patients with neck/back pain, respectively. For further details on the stratified randomisation see Section 4.1.2.

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report (CTR). Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the assumption of superiority of the combination diclofenac + capsaicin versus diclofenac, capsaicin and placebo with regard to the primary efficacy variable 'Change in POM_{WP} between baseline (before application at Visit 1) and Visit 3 (Day 2 evening, 1 hour after application)', which reflects a pain relief on a 0-100 mm VAS about 36 h after baseline.

In a previous study investigating diclofenac in comparison to placebo in patients with acute neck pain, the true treatment difference in POM 48 h after baseline was assumed to be 12 mm [R14-1467] In another study comparing the effects of a combination of comfrey root extract with methyl nicotinate in patients with acute back pain, the standardized difference between the combination and a single ingredient was assumed to be 0.4 [R12-4427].

The sample size for this study is based on an anticipated treatment difference of 12 mm on a 0-100 mm VAS and a common standard deviation of 30 mm, yielding a standardized treatment difference of 0.4 concerning the primary endpoint. The allocation ratio to the

treatment groups diclofenac + capsaicin, diclofenac, capsaicin and placebo is planned to be 3:3:3:1.

A total sample size of 700 patients (210 patients with diclofenac + capsaicin, diclofenac and capsaicin, respectively and 70 patients with placebo will have 98% power to detect a difference of 12 mm on a 0-100 mm VAS for the primary endpoint between treatment effects of diclofenac + capsaicin versus diclofenac and capsaicin, respectively (3:3 allocation ratio) and 82% power to detect the same difference between diclofenac + capsaicin and placebo (3:1 allocation ratio), assuming a common standard deviation of 30 mm and using a 0.05 two-sided significance level.

The total sample size of 700 patients will reach statistical significance with 95% confidence in the 3:3 comparisons (diclofenac + capsaicin versus diclofenac and capsaicin, respectively), when the observed treatment difference is at least 5.7 mm, and in the 3:1 comparison (diclofenac + capsaicin versus placebo), when the observed treatment difference is at least 8.1 mm.

About 800 patients will be randomised to ensure that 700 patients are evaluable for the primary endpoint; as soon as 700 patients in total are evaluable for the primary analysis, the randomisation will be stopped. To ensure that each application site stratum “back pain” or “neck pain” is represented by at least 40% of the randomised patients, randomisation into a respective stratum will be capped as soon as 60% of the total trial population have been allocated to the respective stratum.

Calculations were performed using nQuery Advisor® 6.1 statistical package by Statistical Solutions Ltd.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, relevant BI SOPs, and relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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

The rights of the Investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/ IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

eCRFs for individual patients will be provided by the Sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For eCRF all data need to be derived from source documents.

8.3.2 Direct access to source data and documents

The Investigator/ institution will permit trial-related monitoring, audits, IRB/ IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA/ on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

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

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For capsaicin/diclofenac gel, and active comparators containing the individual components this is the current version of the Investigator's Brochure [c03404356].

For paracetamol the reference document is the SmPC of Panadol Original Tablets®.

The current versions of these reference documents are provided in the ISF. No AE are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IRBs/IECs, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

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

8.6 END OF TRIAL

The end of the trial is defined as last patient last follow-up visit (Visit 7T).

The IEC/ CA in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

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10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		21-Jun-2016
EudraCT number		2015-000404-25
BI Trial number		1358.1
BI Investigational Product(s)		Diclofenac + Capsaicin
Title of protocol		A randomized, controlled multi-centre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title page
Description of change		[redacted] Phone: [redacted] Fax: [redacted] Has been changed to: [redacted]

		Phone: [redacted] Fax: [redacted]
Rationale for change		Change of responsibility
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS – Main criteria for inclusion
Description of change		Sensitivity to algometric pressure on the painful trigger point ≤ 2.5 N/cm² Has been changed to: Sensitivity to algometric pressure on the painful trigger point ≤ **25** N/cm²
Rationale for change		An upper limit of 2.5 N/cm² has turned out to be too low and would only allow the inclusion of patients with extremely high algometric pressure. This upper limit had been taken from Pabst et al. (2013), Phytother. Res. 27: 811–817. However, personal communication was received from [redacted] (co-author of the publication and coordinating investigator of this trial) that actually and upper limit of 2.5 kp/cm² had been applied in the published study. 2.5 kp/cm² correspond to 24.5 N/ cm².
Section to be changed		Flowchart
Description of change		Approximate day time of Visit 7T which was formerly given as “E” (evening) was removed.
Rationale for change		Visit 7T does not need to be performed at a specific day time
Section to be changed		Flowchart
Description of change		Hand-out of patient diary; Instructions on use: X at visit 1 Has been changed to: Return of patient diary: X at visit1, **visit 2, visit 3, visit 4, visit 5**
Rationale for change		The patients get a new diary at each visit 1-5 and are supposed to return that diary at the very next visit
Section to be changed		Flowchart

Description of change		Return of patient diary: X at visit 6 Has been changed to: Return of patient diary: X at **visit 2, visit 3, visit 4, visit 5** and visit 6
Rationale for change		The patients get a new diary at each visit 1-5 and are supposed to return that diary at the very next visit
Section to be changed		Flowchart
Description of change		Completion of patient participation (*) Has been changed to: Completion of patient participation
Rationale for change		Correction of typo
Section to be changed		3.3.2 Inclusion criteria
Description of change		4. Sensitivity to algometric pressure on the painful trigger point ≤ 2.5 N/cm² (see Section 5.2.2). Has been changed to: 4. Sensitivity to algometric pressure on the painful trigger point ≤ **25** N/cm² (see Section 5.2.2).
Rationale for change		An upper limit of 2.5 N/cm² has turned out to be too low and would only allow the inclusion of patients with extremely high algometric pressure. This upper limit had been taken from Pabst et al. (2013), Phytother. Res. 27: 811–817. However, personal communication was received from [redacted] (co-author of the [redacted] dinating investigator of this trial) that actually and upper limit of 2.5 kp/cm² had been applied in the published study. 2.5 kp/cm² correspond to 24.5 N/ cm².
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Patients who discontinue or withdraw from the study after randomisation will be considered as “early discontinuations” and the reason for this premature discontinuation must be recorded in

		the eCRF. The Investigator must inform the sponsor within 24 hours via IRT (see Section 4.1) about any discontinuation of a subject. Has been changed to: Patients who discontinue or withdraw from the study after randomisation will be considered as "early discontinuations" and the reason for this premature discontinuation must be recorded in the eCRF. The Investigator must inform the sponsor within 24 hours (see Section 4.1) about any **premature** discontinuation of a subject.
Rationale for change		The IRT system does not require to register the termination of a patient's trial participation
Section to be changed		Table 4.1.1: 1, table 4.1.1: 2, table 4.1.1: 3, table 4.1.1: 4
Description of change		Semi solid formulation Has been changed to: **Gel**
Rationale for change		Correction
Section to be changed		[redacted]

[redacted]

[redacted]

Section to be changed		Figure 5.2.1:5
Description of change		A downward showing arrow was added to the image
Rationale for change		Added for clarification
Section to be changed		5.3.3 Physical examination
Description of change		A physical examinations will be performed by the Investigator or designated site-personnel at the time point indicated in the Flow Chart. Has been changed to: A physical examination will be performed by the Investigator or designated site-personnel at the time point indicated in the Flow Chart.
Rationale for change		Correction of typo
Section to be changed		Table 5.3.5: 1 Safety laboratory tests
Description of change		baso-phils Has been changed to: basophils
Rationale for change		Correction of typo
Section to be changed		5.3.7 Adverse event collection and reporting
Description of change		From signing the informed consent onwards through the Residual Effect period (REP), all

		AEs (serious and non-serious), and AESIs. Has been changed to: From signing the informed consent onwards through the Residual Effect period (REP), all AEs (serious and non-serious), and AESIs **must be reported**.
Rationale for change		Correction of typo
Section to be changed		6.2.2 Treatment period
Description of change		The 3rd bullet point under "The patient should be instructed" was changed from to refrain from using rescue medication before Visit 3 if possible. If this turns out not to be possible, another supply of rescue medication might be dispensed at visit 3 to to refrain from using rescue medication before Visit 3 if possible. If this turns out not to be possible, another supply of rescue medication might be dispensed at visit **5**
Rationale for change		Correction of typo
Section to be changed		6.2.2 Treatment period
Description of change		The 7th bullet point under "The patient should be instructed" was splitted from • to return their patient's diary as well as all unused trial and rescue medication and packaging at Visit 6 to • **to return their patient's diary at visit 2, visit 3, visit 4, visit 5 and visit 6** • to return all unused trial and rescue medication and packaging at Visit 6
Rationale for change		The patients get a new diary at each visit 1-5 and are supposed to return that diary at the very next visit
Section to be changed		6.2.3 Follow Up Period and Trial Completion

Description of change		All study procedures according to the Flow Chart should be performed. Patients who complete the treatment period should be registered as completed in the IRT system. Has been changed to: All study procedures according to the Flow Chart should be performed.
Rationale for change		The IRT system does not require to register the termination of a patient's trial participation
Section to be changed		6.2.3 Follow Up Period and Trial Completion
Description of change		Patient who want to discontinue the trial treatment prematurely should be asked to have Visit 6 in the morning after the last application of the trial medication and to have a Visit 7T at least 48 hours after that last application. Has been changed to: Patient**s** who want to discontinue the trial treatment prematurely should be asked to have Visit 6 in the morning after the last application of the trial medication and to have a Visit 7T at least 48 hours after that last application.
Rationale for change		Correction of typo
Section to be changed		[redacted]
[redacted]		[redacted] endpoint
[redacted]		[redacted]
Section to be changed		[redacted]
Description of change		[redacted]

		[redacted]
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c03317678 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-2

Title: A randomized, controlled multi-centre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	21 Jun 2016 16:06 CEST
Author-Trial Statistician		21 Jun 2016 16:09 CEST
Approval-Therapeutic Area [redacted]		22 Jun 2016 09:58 CEST
Author-Team Member Medicine		23 Jun 2016 09:18 CEST
Author-Trial Clinical Monitor		24 Jun 2016 15:46 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed