

Clinical Trial Protocol

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EudraCT No.: EU Trial No.:	2016-000902-12	
BI Trial No.:	1335.5	
BI Investigational Product(s):	Ibuprofen + Caffeine	
Title:	A randomized, placebo- and active-controlled multi-country, multi-centre parallel group study to evaluate the efficacy and safety of a fixed dose combination of 400 mg ibuprofen and 100 mg caffeine compared to ibuprofen 400 mg and placebo in patients with acute lower back or neck pain	
Lay Title:	Ibuprofen/caffeine lower back or neck pain study	
Clinical Phase:	III	
Trial Clinical Monitor:	<div style="background-color: black; height: 100px; width: 100%;"></div> Phone: [REDACTED] Fax: [REDACTED]	
Coordinating Investigator:	<div style="background-color: black; height: 100px; width: 100%;"></div> Phone: [REDACTED] Fax: [REDACTED]	
Status:	<u>Final Protocol</u>	
Version and Date:	Version: 2.0	Date: 05 August 2016
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		NA	
Name of active ingredient:			Ibuprofen + Caffeine
Protocol date: 28-July-2016	Trial number: 1335.5		Revision date: 05-August-2016
Title of trial:			A randomized, placebo- and active-controlled multi-country, multi-centre parallel group study to evaluate the efficacy and safety of a fixed dose combination of 400 mg ibuprofen and 100 mg caffeine compared to ibuprofen 400 mg and placebo in patients with acute lower back or neck pain
Coordinating Investigator:	[REDACTED]		
	Phone: [REDACTED] Fax: [REDACTED]		
Trial site(s):	Multi-centre trial, conducted in 2 countries (Germany, Russia)		
Clinical phase:	III		
Objective(s):	<p>To assess the efficacy and safety of a 400 mg ibuprofen/100 mg caffeine tablet in comparison to a 400 mg ibuprofen tablet for the treatment of acute lower back or neck pain</p> <p>The primary objective of this trial is to demonstrate superior efficacy of the combination 400 mg ibuprofen/100 mg caffeine versus 400 mg ibuprofen and placebo.</p> <p>A secondary objective is to assess the safety and tolerability of a 400 mg ibuprofen/100 mg caffeine tablet in comparison to a 400 mg ibuprofen tablet, and a placebo tablet.</p>		

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Name of company:	Boehringer Ingelheim		
Name of finished product:	NA		
Name of active ingredient:	Ibuprofen + Caffeine		
Protocol date: 28-July-2016	Trial number: 1335.5		Revision date: 05-August-2016
Methodology:	Randomised, double-blind, placebo- and active-controlled, multi-country, multi-centre 3-arm parallel group study		
No. of patients:	650 randomized		
Total entered:	Approximately 650 randomized to achieve 600 patients eligible for assessment of the primary endpoint		
Each treatment:	Ibuprofen/caffeine: 260 Ibuprofen: 260 Placebo: 130		
Diagnosis :	Acute lower back or neck pain		
Main criteria for inclusion:	Male or female patients \geq 18 years with current diagnosis of acute lower back or neck pain for at least 24 hours but less than 21 days. Acute lower back pain resulting in pain on movement (POM) \geq 5 on a 0-10-point Numerical Rating Scale (NRS) for at least one POM procedure out of the 5 standardized procedures. Sensitivity to algometric pressure on the painful trigger point \leq 25 N/cm ²		
Test product:	400 mg ibuprofen and 100 mg caffeine tablet		
Dose:	One tablet three times daily with intervals of 6-8 h hours over 5 days (up to Day 6 morning)		
Mode of administration:	p.o.		

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Comparator products:	400 mg ibuprofen tablet placebo tablet		
Dose:	One tablet three times daily with intervals of 6-8 h hours over 5 days (up to Day 6 morning)		
Mode of administration:	p.o.		
Duration of treatment:	5 days		
Endpoints	<p>Primary endpoint:</p> <ul style="list-style-type: none">Change in Pain On Movement (POM) with regard to the Worst Procedure (WP), i.e. the procedure with the highest pain score at baseline (POM_{WP}), between baseline (Day 1 morning pre-dosing) and Day 2 morning, 2 hours after drug intake. <p>Key Secondary endpoints:</p> <ul style="list-style-type: none">Area Under the Curve (AUC) for POM_{WP} between baseline and the morning of Day 4 (POM_{WP}AUC_{72h})AUC for POM_{WP} between baseline and the morning of Day 6 (POM_{WP}AUC_{120h}) <p>Other secondary endpoints:</p> <ul style="list-style-type: none">Change in Pressure Algometry (PA) between baseline and Day 2 morning, 2 hours after drug intakeGlobal assessment of efficacy by the patient at the end of treatment (Day 6 morning)Number of patients with a decrease in POM_{WP} of at least 30% between baseline and Day 2 morning, 2 hours after drug intake		

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		<ul style="list-style-type: none">Number of patients with a decrease in POM_{WP} of at least 50% between baseline and Day 2 morning, 2 hours after drug intakeTime to first meaningful POM_{WP} relief within 2 hours after the first dose of study medication			
Safety criteria:	<ul style="list-style-type: none">Incidence of adverse events (AEs) and serious AEs (SAEs)Laboratory test abnormalities 				
Statistical methods:	<p><u>Primary endpoint:</u> For the analysis of the change in POM_{WP} between baseline and Day 2 morning, 2 hours after drug intake, 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 and the stratification factors country and wp-site (back/neck) as discrete fixed effects, baseline POM_{WP} as a continuous fixed effect, and interaction between time and treatment as well as interaction between baseline POM_{WP} and time. The primary treatment comparison will be the contrast between treatments at the endpoint time, respectively.</p>				

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For the analysis of the primary endpoint with regard to the strata concerning wp-site (back / neck), separate models will be performed as described above, but excluding the factor wp-site, respectively.		<p>Key-secondary endpoints: POM_{WP}AUC_{72h} and POM_{WP}AUC_{120h} will be analysed using analysis of covariance including treatment and country and wp-site (back/neck) as fixed categorical effects and the baseline POM_{WP} as a continuous covariate.</p> <p>Other secondary endpoints: The change in PA between baseline and Day 2 morning, 2 hours after drug intake will be analysed using analysis of covariance including treatment, country and wp-site (back/neck) as fixed categorical effects and the baseline PA as a continuous covariate.</p> <p>The global assessment of efficacy by the patient at the end of treatment (Day 6 morning) as well as the number of patients with a decrease in POM_{WP} of at least 30% or 50%, respectively, from baseline until Day 2 morning, 2 hours after drug intake, will be analysed by a logistic regression model, including the factor treatment and the categorical stratification factors country and wp-site (back/neck).</p> <p>For the time to the first meaningful POM_{WP} relief a Kaplan-Meier analysis will be performed and the log-rank test stratifying for the categorical variables country and wp-site (back/neck) will be used.</p>	

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For the analysis of the key- and other secondary endpoints with regard to the strata concerning wp-site (back / neck), separate models will be performed as described above, but excluding the factor wp-site, respectively.			

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FLOW CHART

Trial Periods	Screening Period	Treatment period			EOT	FU¹⁰
		1	2	3		
Visit	1	1⁵	2	3	4	5
Days	1	1⁵	2	4	6	8-10
Time window for visits	none	none	none	± 1 Day	± 1 Day	none
Informed consent ⁴	X					
Demographics	X					
Medical history	X					
Physical examination	X				X	
Vital signs	X				X	
Safety Laboratory Tests	X				X	
12 lead-ECG	X				X	
Review of in-/exclusion criteria	X					
Randomization via Interactive Response Technology (IRT) ¹³		X				
Dispense trial drugs		X				
Distribute Patient Diary and Instruct Patient		X				
POM _{WP} relief score ⁹	X	X	X		X	
[REDACTED]						
[REDACTED]						
[REDACTED]						
Administer trial drugs ¹		X ²	X	X	X ³	
Pregnancy Testing (Urine) ¹⁴	X				X	
Pain On Movement (POM) ₇	X	X	X	X	X	
Pressure Algometry (PA)	X	X	X	X	X	
Rescue Medication ⁸		X	X	X	X	
Adverse events	X	X	X	X	X	X
[REDACTED]						
Compliance check			X	X	X	
Concomitant therapy	X	X	X	X	X	X
Global Assessment of efficacy by the patient and investigator					X	
Collect patient Diary and enter data onto eCRF					X	
[REDACTED]						
Completion of patient participation						X ⁶

¹ Study drug administered TID with doses 6-8 hours apart

² First dose of study drug administered in clinic by the patient in the presence of investigator

³ Last dose of study drug taken on the morning of Day 6, 1-3 hours before clinic visit starts

⁴ Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions

⁵ Day of Randomization / Day of first intake of randomised medication

⁶ Completion of patient participation also needs to be completed if the patient withdraws prematurely following randomization. (see [Section 3.3.4](#))

⁷ The POM evaluation at each visit should be in the morning (7:00-10:00) 2 hours after intake of study drug. POM will be assessed by the patient using a 0-10-point Numerical Rating Scale (NRS). Baseline POM will be assessed using five standard procedures and the procedure which results in highest POM (Worst Procedure, POM_{WP}) will be repeated for an individual patient at the subsequent visits

⁸ Patients will be encouraged not to take rescue medication (paracetamol) until after the primary endpoint is assessed on Day 2. On subsequent days of the study, patients should take only a maximum dose of 2 grams paracetamol over a 24 hour period and doses should be at least 4 hours apart. The patient will record the date, time and dosage of rescue medication in the diary

⁹ The procedure which results in highest POM at baseline (POM_{WP}) will be repeated by the same site staff member 10, 20, 30, 60 and 120 min after the first dose of study medication. The POM_{WP} Relief Score will be assessed by the patient at each of these time points by using a 5-point Verbal Rating Scale (VRS) (0= no POM_{WP} relief ; 1= a little or perceptible POM_{WP} relief ; 2= meaningful POM_{WP} relief ; 3= a lot of POM_{WP} relief ; 4=complete POM_{WP} relief)

¹⁰ 2-4 Days after visit 4 at the follow up Visit 5(FU) an interview by telephone is conducted with the patient to determine REP and post treatment safety status

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

¹³ During randomization patients will be stratified by country and by whether the patients have back (worst pain with procedure 4 or 5) or neck pain (worst pain with procedure 1, 2 or 3)

¹⁴ A urine pregnancy test must be negative in women of childbearing potential at the screening visit just prior to randomisation and at the last clinic visit

¹⁵ 2-4 Days after visit 4 at the follow up Visit 5 (FU) an interview by telephone is conducted with the patient to determine whether headache was perceived after end of study treatment

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AMP	Auxiliary Medical Products
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
GCP	Good Clinical Practice
HPC	Human Pharmacology Center
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
LoEE	List of Essential Element
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Sub team
N/cm ²	Newton/square centimetre
NIMP	Non-Investigational Medical Products
NRS	Numerical Rating Scale
OPU	Operative Unit
PA	Pressure Algometry
PD	Pharmacodynamics

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PI	Pain Intensity
PK	Pharmacokinetics
p.o.	per os (oral)
POM	Pain on Movement
POM _{WP}	Pain on Movement, Worst procedure
PCC	Protocol Challenge Committee
q.d.	quaque die (once a day)
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
SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d., TID	ter in die (3 times a day)
TMF	Trial Master File
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
VRS	Verbal Rating Scale
WP	Worst Procedure (= procedure with highest POM-value)
WP-site	Site with the worst procedure (site = neck for procedures 1-3; site = back for procedures 4 and 5)

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

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that is one of the most widely used over-the-counter (OTC) medications around the world. Orally administered ibuprofen was initially approved as an OTC analgesic in the United States in 1984. The favourable efficacy and safety profile of OTC ibuprofen has been well established over its more than 28 year history of usage. Studies have shown that 400 mg of ibuprofen is a very effective analgesic, more effective than acetaminophen 1000 mg and aspirin 1000 mg ([P02-05388](#), [P90-0404](#), [P05-00433](#), [P02-05406](#), [R99-0976](#), [P13-03158](#)). However, there are individuals who don't get sufficient pain relief with currently available single ingredient analgesic products. The combination of ibuprofen 400 mg and caffeine 100 mg is currently being evaluated as a potentially more efficacious treatment for those consumers who do not experience adequate pain relief with maximum single doses of single ingredient analgesic products. Based on published studies, it is expected that caffeine will provide an adjuvant effect to ibuprofen and enhance its efficacy. Caffeine has been shown to potentiate analgesic activity probably through a central nervous system (CNS) mechanism of action ([P12-12821](#), [P11-05389](#)).

1.2 DRUG PROFILE

Caffeine is the most widely consumed psycho-stimulant drug. It is almost completely absorbed in the gastrointestinal tract. Since it is lipid soluble, it is rapidly absorbed into the brain, where its mild CNS effects, which include increased wakefulness, alertness, and endurance, begin to work in 6-8 minutes ([P12-14205](#), [P93-75428](#)). Pre-clinical studies in rodents suggest that caffeine has weak analgesic effects. These studies suggest that caffeine's anti-nociceptive effects may be attributed to the blockade of adenosine receptors, inhibition of cyclo-oxygenase 2 enzyme synthesis, or potentially by changes in emotional status ([P07-08407](#), [P93-75428](#), [P06-04171](#)).

Because of its rapid absorption/distribution and CNS/analgesic effects, caffeine has been used in combination with both prescription and over-the-counter (OTC) analgesics for many years. These combination products have met widespread consumer acceptance. Studies in several pain models have demonstrated the analgesic adjuvant effect of caffeine when combined with a variety of analgesics ([P10-10394](#), [R98-0795](#)). A recently completed Cochrane review of 19 randomised, double-blind, well controlled studies, involving 7,238 patients, concluded that the addition of caffeine at doses 100 mg or greater to standard doses of commonly used analgesics provides an increase in the proportion of patients who experience a good level of pain relief ([P12-04063](#)). The addition of less than 65 mg of caffeine to analgesics is generally thought to be ineffective.

The Cochrane review included four published studies evaluating the combination of ibuprofen and caffeine. An oral surgery study demonstrated the effectiveness of caffeine 100 mg as an analgesic adjuvant to ibuprofen 100 mg and 200 mg ([P02-05324](#)). In that study, caffeine was found to increase the potency of ibuprofen by 140-180%. Similar results were obtained in a post-episiotomy model ([P84-98710](#)). In another oral surgery study, caffeine (50 mg, 100 mg, and 200 mg) increased the analgesic effect and provided an earlier onset of analgesic effect of ibuprofen 200 mg ([R97-2392](#)). There were no differences between the three doses of caffeine in that study. In patients with tension type headache, ibuprofen 400 mg combined with caffeine 200 mg was shown to provide superior efficacy compared to each ingredient alone, and placebo ([P02-05407](#)). The median time to perceptible and meaningful headache improvement was faster with the combination product compared to ibuprofen alone and placebo. Eighty percent of patients receiving the combination experienced a meaningful improvement in headache compared with 67% receiving ibuprofen alone.

For a more detailed description of the study drug profile please refer to the current Investigator's Brochure (IB) ([c02098879-06](#)) and for Paracetamol used as rescue medication the reference document is the product SmPC.

The present study is being conducted to assess the analgesic efficacy of ibuprofen 400 mg combined with caffeine 100 mg compared to ibuprofen 400 mg alone and placebo in the treatment of acute neck or back pain. In order to provide a more complete assessment, safety and efficacy will be assessed following multiple dose administration over a six-day evaluation period.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The combination of ibuprofen and caffeine is being evaluated as a potentially more efficacious analgesic for patients who do not experience adequate pain relief with a single ingredient analgesic product. Based on published studies, it is expected that 100 mg of caffeine will provide an adjuvant effect to ibuprofen 400 mg, as caffeine at doses ranging from 50 mg to 200 mg has been shown to provide faster and/or better pain relief than ibuprofen doses of 100 mg to 400 mg alone. ([P02-05407](#), [P02-05324](#), [R97-2392](#), [P84-98710](#), [U13-3353-02](#)).

2.2 TRIAL OBJECTIVES

To assess the efficacy and safety of a 400 mg ibuprofen/100 mg caffeine tablet in comparison to a 400 mg ibuprofen tablet for the treatment of acute lower back or neck pain.

The primary objective of this trial is to demonstrate superior efficacy of a 400 mg ibuprofen/100 mg caffeine tablet over a 400 mg ibuprofen tablet and a placebo tablet.

A secondary objective is to assess the safety and tolerability of a 400 mg ibuprofen/100 mg caffeine tablet in comparison to a 400 mg ibuprofen tablet and a placebo tablet.

2.3 BENEFIT - RISK ASSESSMENT

Many patients who use currently marketed OTC pain relievers find that no single analgesic agent can completely relieve their moderate to severe acute pain ([P12-04607](#)). A ceiling effect is obtained with currently available analgesics such as ibuprofen and acetaminophen and increasing dosages produce little or no analgesic benefit, but increase the risk of adverse effects. Therefore, there is an unmet patient need for a superior OTC analgesic with a favourable safety profile. Combining an analgesic such as ibuprofen with caffeine, a known analgesic adjuvant, is intended to provide superior efficacy to either ingredient alone without increasing the risk of side effects. In addition, an analgesic with superior efficacy may reduce the need for additional doses of analgesics, thereby reducing the total amount of analgesics consumed leading to an improved benefit risk ratio.

The safety profiles of ibuprofen and caffeine have been well established over their many years of use. Given that combination products containing caffeine have been marketed in various parts of the world for many years, there are no data to suggest that the combination of ibuprofen and caffeine will have a safety profile unlike that of the individual ingredients. A summary of the potential risks and benefits of ibuprofen combined with caffeine, as well as with each individual ingredient is provided in the Investigator's

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Brochure (IB) ([c02098879-06](#)). The investigator must become familiar with all sections of the current IB before the start of the study.

In order to minimize the risk of adverse events (AE) and maximize the benefit of adequate pain relief for patients participating in this trial, all patients will undergo a physical examination and safety laboratory testing to ensure that they are healthy enough to participate in the study. In addition, females of child bearing potential will receive a urine pregnancy test at screening in order to ensure that the female patient is not pregnant. Individuals at increased risk of developing gastrointestinal (GI) adverse events associated with the use of NSAIDs will be excluded from the study. The safety of patients enrolled into the study will be monitored by study personnel during the throughout the entire study. Adverse and serious adverse events are being reported from the time the patient signs the informed consent, until the last visit of the study.

Although rare, a potential for drug-induced liver injury (DILI) 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 information on DILI in [section 5.3.7.1](#).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

3.1.1 Administrative structure of the trial

This trial is a multi-centre, double-blind, randomised, parallel-group study comparing the effect of the fixed dose combination of ibuprofen 400 mg and caffeine 100 mg versus ibuprofen 400 mg and placebo in patients of at least 18 years of age with acute neck or back pain. Approximately 650 patients will be randomized in a ratio of 2:2:1:

After a screening evaluation at Visit 1, eligible patients will be randomised.

Patients are initially treated at the site with the first of three doses at least 6-8 hours apart over the initial 24 hours with a tablet containing ibuprofen 400 mg + caffeine 100 mg, or ibuprofen 400 mg or placebo. The patients will be examined after the initial 24 hour period at visit 2 on Day 2 at the study, 1-3 hours after taking their morning dose of study drug on Day 2. The patients will be encouraged not to take rescue medication before the primary endpoint is assessed on Day 2.

After the visit 2 assessments have been completed patients will continue to be treated with their assigned blinded treatment administered TID at least 6-8 hours apart over the remainder of the 6 day dosing period of the study.

The study will include the following visits: Screening and initial dosing visit (Visit 1 on Day 1) primary endpoint assessment visit (Visit 2 on Day 2), a Visit 3, Day 4 clinic visit and an End-of-Treatment Visit (Visit 4 on Day 6). In addition there will be a follow up by telephone (Visit 5), 2-4 days after the EOT Visit.

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

The study will be a multi-center study and is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multi-center trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

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

The organisation of the trial in the participating countries will be performed by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to agreed-upon SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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 ISF.

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

This trial has been designed to assess the acute effect of a fixed dose combination (FDC) of ibuprofen plus caffeine in patients with back or neck pain. The pain on movement (POM) assessment has been recognized as a reliable design for showing efficacy of new acute pain treatments. ([R14-1467](#)).

The effects of the FDC will be compared to ibuprofen alone, and placebo to prove efficacy, as well as the superiority over ibuprofen alone and placebo treatments. Then, patients will continue to receive assigned treatment over a total of 6 days of treatment. This design will assess the efficacy after the first day of dosing based on the current knowledge about the efficacy of ibuprofen for the treatment of acute pain ([see Section 1.1](#)). Also, the tolerability and efficacy will be evaluated throughout 6 days of treatment. Study medication may be taken as early as every 6 hours and no later than every 8 hours, up to 3 times daily while awake.

The allocation to treatment will be done in a 2:2:1 ratio for ibuprofen plus caffeine, ibuprofen and placebo with a total sample size of 650 patients. This distribution and sample size should have sufficient power to demonstrate a difference of the FDC versus the Ibuprofen and placebo arms.

3.3 SELECTION OF TRIAL POPULATION

Approximately 650 male or female patients of at least 18 years of age with a current diagnosis of acute back or neck pain for at least 24 hours. Patients with acute back or neck pain resulting in pain on movement (POM) ≥ 5 on a 0-10-point Numerical Rating Scale will be randomly assigned in a 2:2:1 ratio to each of the following treatment arms:

Ibuprofen + caffeine

Ibuprofen

Placebo

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the investigator site file (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

Otherwise healthy individuals with acute back or neck pain for at least 24 hours not due to a specific diagnosis are required for this 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 who are ≥ 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 POM ≥ 5 on a 0-10-point NRS for at least one POM procedure out of 5 standardized procedures.
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).

6. Reliable, cooperative, and of adequate intelligence to record the requested information on the analgesic questionnaires.
7. Examined by the attending physician and medically cleared to participate in the study.
8. In good general health, with a body mass index (BMI) < 30, and have no contraindications to any of the study medications.

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. Patients with pain at rest ≥ 9 . (0-10 NRS scale).
3. Patients with pain at rest ≥ 9 . (0-10 NRS scale).
4. Patient with chronic back or neck pain as defined as pain for 3 weeks or longer.
5. Back or neck pain that is attributable to any identifiable cause (e. g. disc prolapse, spondylolisthesis, osteomalacia, inflammatory arthritis, metabolic, neurological diseases or tumour).
6. Any strains of the back or neck muscles documented by clinical evaluation and anamnesis that occurred 21 days to 3 months prior to the screening visit.
7. Surgery due to back or neck pain or rehabilitation due to back or neck pain in the last 12 months.
8. 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) for the same indication or other indications.

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

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

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.

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

11. Patients taking CNS or other psychotropic drugs, or any nutritional supplement known to have psychotropic effects such as St. John's Wort, Chapparal, Comfrey, Germander, Gin Bu Huan, Kava, Pennyroyal Skullcap, or Valerian within two months of taking the first dose of study medication. Patients who have been on stable doses of these medications for at least two months will be allowed into the study, as long as they maintain this dose throughout the study, and their condition is judged stable by the Principal Investigator.

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

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

14. Patient not able to understand and comply with trial requirements based on investigators judgment.

15. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within timeframe of this study.

16. Patients who must or wish to continue the intake of restricted medications ([see section 4.2.2.1](#)) or any drug considered likely to interfere with the safe conduct of the trial.

17. Previous enrolment in this trial.

18. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).

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19. Habituation to analgesic drugs or caffeine (i.e., routine use of oral analgesics 5 or more times per week or ingestion of 4 or more caffeine-containing drinks daily); use of "high energy" drinks more than once per week.
20. History of allergic reaction (e.g., asthma, rhinitis, swelling, shock, or hives) to acetaminophen, ibuprofen, naproxen, aspirin, celecoxib, or any other NSAID or caffeine.
21. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial.
22. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
23. Prior use of any type of analgesic or NSAID within 5 half-lives of that drug before initial dosing in the trial.
24. Presence or history (within 2 years of enrolment) of bleeding disorder or peptic ulcer disease.
25. Has a clinically significant abnormal electrocardiogram (ECG) at screening as determined by the investigator.
26. Has known impaired liver function, e.g., serum ALT, AST, alkaline phosphatase, or GGT greater than 2.5 times the upper limit of normal, or BUN, creatinine, or bilirubin greater than 1.5 times the upper limit of normal without a known benign explanation.
27. The patient is a member of the study site staff either directly involved with the study, an employee of the Sponsor, or a relative of study site personnel directly involved with the study or Sponsor.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice.

The investigator may terminate a patient from the study at any time for lack of therapeutic effect that is intolerable to the patient or otherwise considered unacceptable, for intolerable or unacceptable AEs, inter-current illness, non-compliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the patient's best interest.

If a patient is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate electronic case report form (e-CRF). Whenever possible and

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reasonable, the evaluations which were to be conducted at the completion of the study should be performed at the time of premature discontinuation and at the telephone follow up visit.

Every effort will be made to continue safety monitoring and collection of safety data even if the patient chooses to discontinue from the study or is prematurely terminated from the study.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at the single centre,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial,
3. Violation of GCP, the CTP, or the contract by the trial site or investigator, disturbing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

1. Ibuprofen + Caffeine, 400mg/100mg film coated tablets
2. Ibuprofen, 400mg film coated tablets
3. Ibuprofen Placebo, film coated tablets

Through the use of ibuprofen placebo tablets, all treatments will appear identical. Patients will take the assigned dose three times daily, by mouth, for every 6-8 hours

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are as shown in [Tables 4.1.1: 1](#) to [3](#).

Table 4.1.1: 1 Ibuprofen-caffeine

Substance	Ibuprofen + Caffeine
Pharmaceutical formulation	Tablet
Source	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength	400 mg ibuprofen + 100 mg caffeine
Posology	3 times daily 6-8 hours apart
Route of administration	Per os

Table 4.1.1: 2 Ibuprofen

Substance	Ibuprofen
Pharmaceutical formulation	Tablet
Source	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength	400 mg ibuprofen
Posology	3 times daily 6-8 hours apart
Route of administration	Per os

Table 4.1.1.3

Ibuprofen Placebo

Substance	Placebo
Pharmaceutical formulation	Tablet
Source	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength	0 mg
Posology	3 times daily 6-8 hours apart
Route of administration	Per os

4.1.2 Selection of doses in the trial

Ibuprofen 400 mg is the maximum single dose of ibuprofen approved without a prescription in many countries throughout the world. Caffeine 100 mg was chosen to be combined with ibuprofen 100 mg since published studies have suggested that it is an analgesic adjuvant to ibuprofen 400 mg.

4.1.3 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 such as whether the patient was in Russia or Germany and whether the patient had back pain (worst pain with procedure 4 or 5) or neck pain (worst pain with procedure 1, 2 or 3). 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 2:2:1 ratio, to either:

- (i) ibuprofen + caffeine
- (ii) ibuprofen
- (iii) placebo

For further details refer to [Section 7.6](#). Entry into the application site stratum . tructions and/randomized use of IRT, which will takeny countries throughout the world. Caffeine 100 mg was chosen to be combined with ibuprofen 100 mg since published studies have suggested that it soon as 58% (about 350 patients) of the total trial population has 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 will be given to the patient and the number of the kit that was dispensed will be entered in the eCRF. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.4 Drug assignment and administration of doses for each patient

At time of randomization at Visit 1, one medication kit containing blisters with all tablets to be administered during the treatment period over 6 days will be dispensed to the patient. The blister packs will be labelled with the medication number assigned by IRT.

Patients will take one tablet every 6-8 hours over each 24 hour period from Day 1 after randomization until the morning of Day 6.

Administration of the initial dose of study drug at Day 1 (Visit 1) will be under supervision of the investigating physician or a designee at the study centre.

4.1.5 Blinding and procedures for un-blinding

4.1.5.1 Blinding

Patients, investigator and everyone involved in analysing or with an interest in this double-blind study will remain blinded with regard to the randomised treatment assignments until after database lock. The randomisation code will be kept secret by Clinical Trial Support up to database lock.

4.1.5.2 Un-blinding and breaking the code

An emergency un-blinding will be available to 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 in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break for a patient is opened, the sponsor must be informed immediately. The reason for un-blinding must be documented on the appropriate eCRF page along with the date and the initials of the person who un-blinded the patient.

The investigator /pharmacist/investigational drug storage manager may un-blind a patient. The blind should be broken only if knowledge of this information may affect treatment of the patient. Every effort must be made to contact the sponsor prior to breaking the blind. Once un-blinded, a patient will be ineligible for any further drug assignments and must be withdrawn from the trial.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI to a designated CRO. Investigational product will be packaged in blister packs 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.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies, which will be provided by the sponsor, must be kept in a secure, limited access storage area under the storage conditions as follows: Store at 25 °C, temporary excursions permitted between 15-30 °C. A temperature log will be maintained to make certain that the drug supplies are stored at the correct temperature.

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 or pharmacist or investigational drug storage manager will receive the investigational drugs 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 or pharmacist or 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 or pharmacist or 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 CRO, the investigator or pharmacist or 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.

The investigator or pharmacist or 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 warehouse or drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse or drug distribution centre will maintain records of the disposal.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Paracetamol tablets (500 mg tablets) will serve as the only 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](#)). Paracetamol will be supplied by the site to the patient at Visit 1. Following the first administration 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 concepts 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 2 when the primary endpoint is assessed. 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. Another supply of rescue medication might be dispensed at another site visit, if required.

There are no special emergency procedures to be followed in this study.

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). Prior to the determination of the primary endpoint on day 2 in addition to other restricted concomitant medications topical analgesic agents such as ice will not be allowed. All concomitant medications used will be recorded in the source document and on the e-CRF.

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. Please also review exclusion criterion 10 regarding patients taking CNS or other psychotropic drugs or any nutritional supplements knowing to have psychotropic effects.

4.2.2.2 Restrictions on diet and life style

Patients should not ingest any caffeine-containing beverages, chocolate, or alcohol throughout the 6 days of the study.

4.2.2.3 Restrictions regarding women of childbearing potential

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

4.3 TREATMENT COMPLIANCE

Patients will be asked to return all unused study medication and empty medication containers, as well as their diaries when they come to the clinic for all study visits. At those visits, the study coordinator, or appropriate designee, will review the diary, and count all returned study medication to reconcile medication use. Patients will be queried if any discrepancies are noted. Based on tablet counts, treatment compliance will be calculated as the number of tablets taken, divided by the number of tablets which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

If the number of doses taken is not between 80-120%, site staff will explain the patient the importance of treatment compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is the change in Pain On Movement (POM) with regard to the Worst Procedure (WP), i.e. the procedure with the highest pain score at baseline (POM_{WP}), between baseline (Day 1 morning pre-dosing) and Day 2 morning, 2 hours after drug intake.

POM is assessed by the patient on one standardized movement by using a Numerical Rating Scale (NRS) ranging from 0 = 'no pain' to 10 = 'worst pain possible for this condition'.

5.1.2 Secondary Endpoints

5.1.2.1 Key-secondary Endpoints

- $POM_{WP}AUC_{72h}$

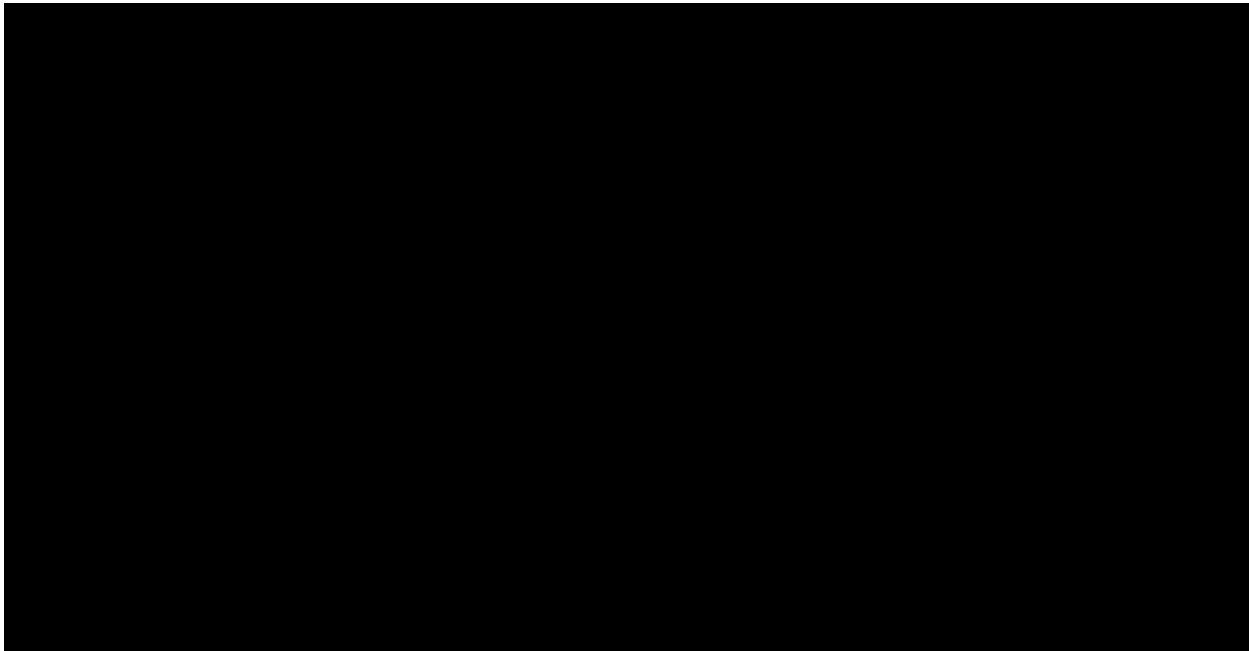
The AUC will be calculated as area under the curve from zero (baseline POM_{WP}) to 72 hours (POM_{WP} in the morning of Day 4) using the trapezoidal rule divided by the observation time. The dates and times of study drug intake related to the POM_{WP} assessments will be the basis for the calculation of respective time intervals.

- $POM_{WP}AUC_{120h}$

The AUC will be calculated as area under the curve from zero (baseline POM_{WP}) to 120 hours (POM_{WP} in the morning of Day 6) using the trapezoidal rule divided by the observation time. The dates and times of study drug intake related to the POM_{WP} assessments will be the basis for the calculation of respective time intervals.

5.1.2.2 Other secondary Endpoints

- Change in Pressure Algometry (PA) between baseline and Day 2 morning, 2 hours after drug intake
- Global assessment of efficacy by the patient at the end of treatment (Day 6 morning)
- Number of patients with a decrease in POM_{WP} of at least 30% between baseline and Day 2 morning, 2 hours after drug intake
- Number of patients with a decrease in POM_{WP} of at least 50% between baseline and Day 2 morning, 2 hours after drug intake
- Time to first meaningful POM_{WP} relief within 2 hours after the first dose of study medication



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 Numerical Rating Scale (NRS) ranging from 0 = 'no pain' to 10 = '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.

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



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.

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.



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.

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



4) Musculus erector spinae (lower part)

Position: The patient lies with his/her front on a small 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.

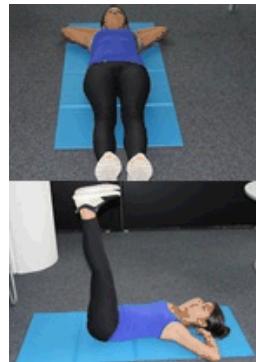
Test: The patient bends his/her legs to reach a square angle, lifts his/her thighs up towards the horizontal line.



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.

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



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 0-10NRS each. For each procedure performed, the patient will assess the pain intensity on the NRS, respectively. The form will be collected after each assessment, so that the patient will not see his/her previous POM assessment. 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 (Worst Procedure, POM_{WP}) will be repeated for an individual patient 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.

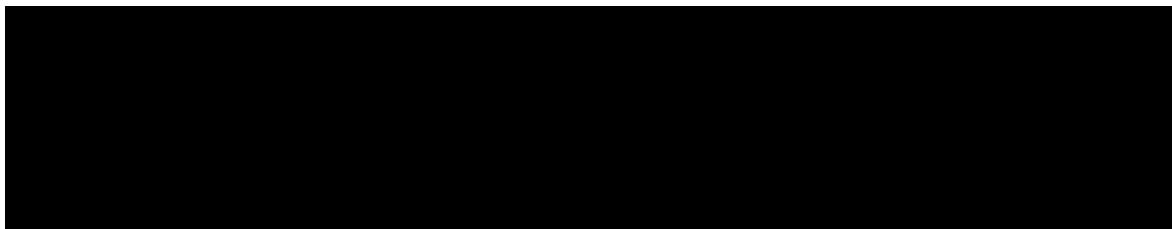
5.2.2 Pressure algometry

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 cm^2 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.

5.2.3 Time to first meaningful pain relief

The procedure which results in highest POM at baseline (POM_{WP}) will be repeated by the investigator 10, 20, 30, 60 and 120 min after the first dose of study medication. The POM_{WP} relief Score ($POM_{WP}RS$) will be assessed by the patient at each of these time points by using a 5-point Verbal Rating Scale (VRS) (0= no POM_{WP} relief ; 1= a little or perceptible POM_{WP} relief ; 2= meaningful POM_{WP} relief ; 3= a lot of POM_{WP} relief ; 4=complete POM_{WP} relief).

The time to first meaningful POM_{WP} relief will be the earliest assessment time point after the first application of the trial medication at which the patient reports a **score of ≥ 2** .



5.2.5 Global assessment of efficacy by the patient

The patient [REDACTED] will assess the overall efficacy of the trial treatment on a 4-point verbal rating scale by answering the question: "How would you rate the overall effect of the study medication for relieving back or neck pain?" (0 = poor; 1 = fair; 2 = good; 3 = very good). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.3 ASSESSMENT OF SAFETY

5.3.1 Endpoints of safety

- Incidence of adverse events (AEs) and serious AEs (SAEs)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

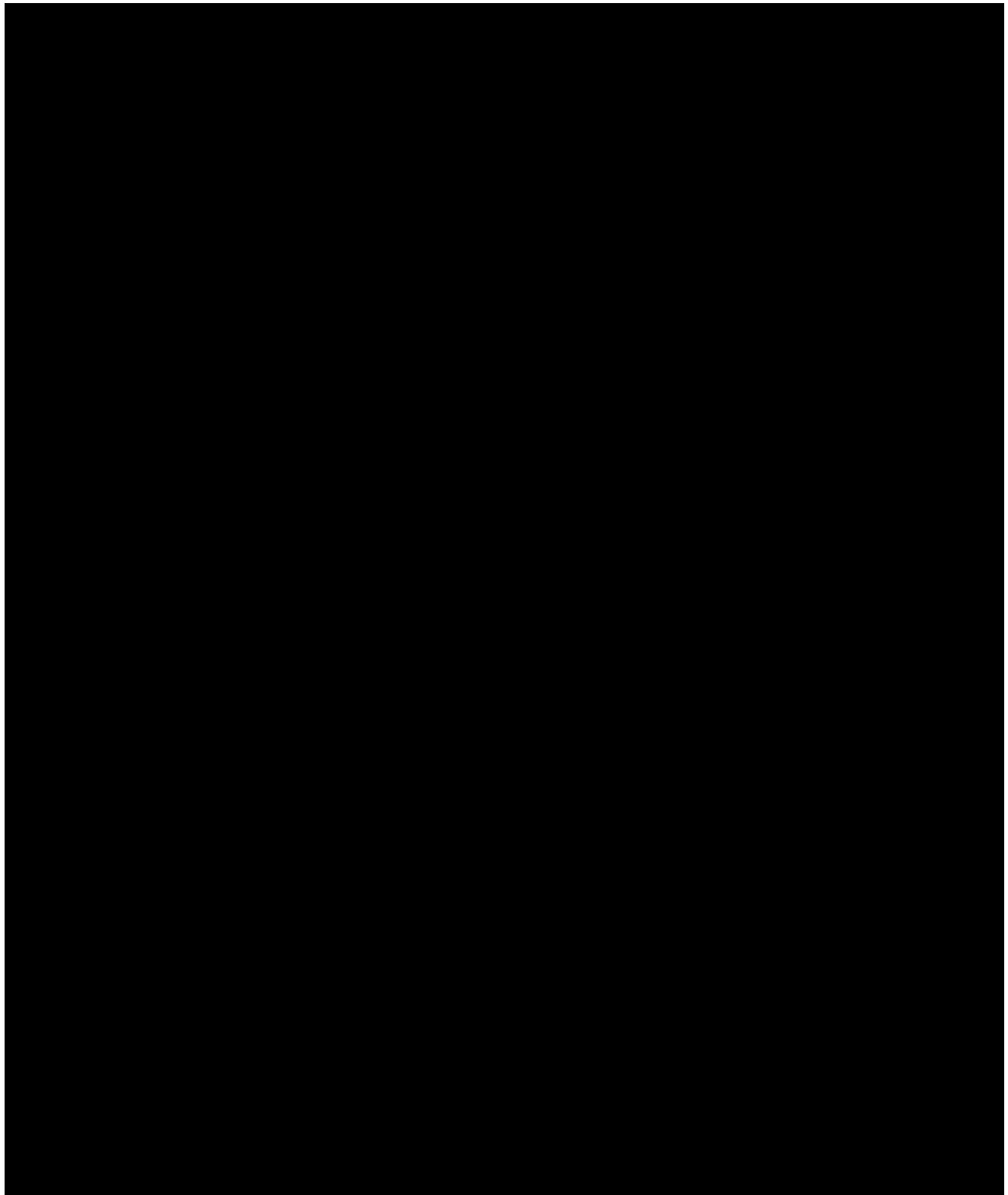
[REDACTED]

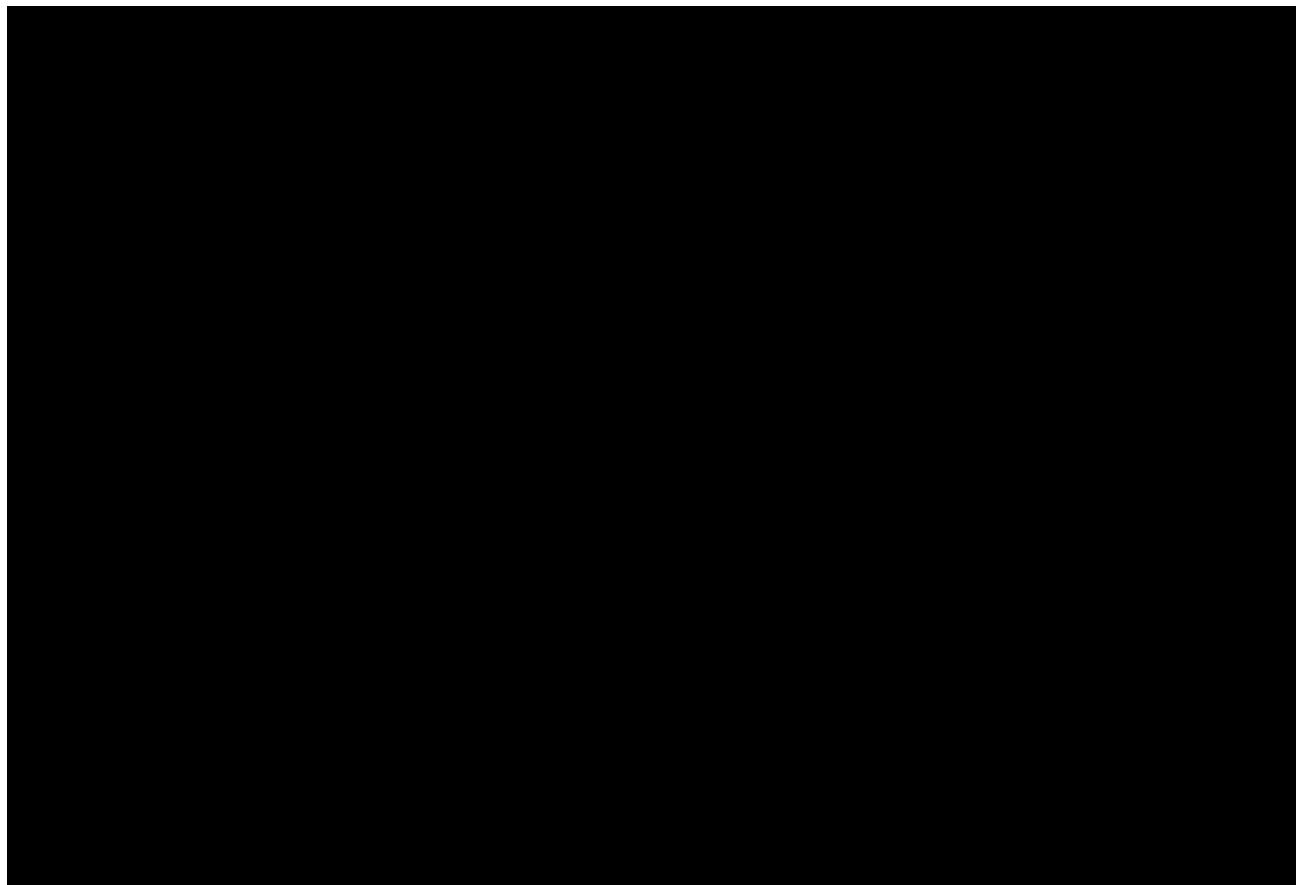
[REDACTED]

[REDACTED]

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5.3.7 Assessment of adverse events

5.3.7.1 Definitions of AEs

Adverse event

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

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

Adverse reaction

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

Serious adverse event

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

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. 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 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 RDC. 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, please [see section 5.3.7.2](#).

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 in the RDC.

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.

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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.

5.3.7.2 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 CRF(s) by the Investigator:

- From signing the informed consent onwards, through the Residual Effect Period (REP) of 24 hours after the last dose of study drug administered, until individual patient's end of trial:
-all AEs (serious and non-serious) and all AESIs
However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits incl. 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.
- After the individual patient's end of trial:
the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

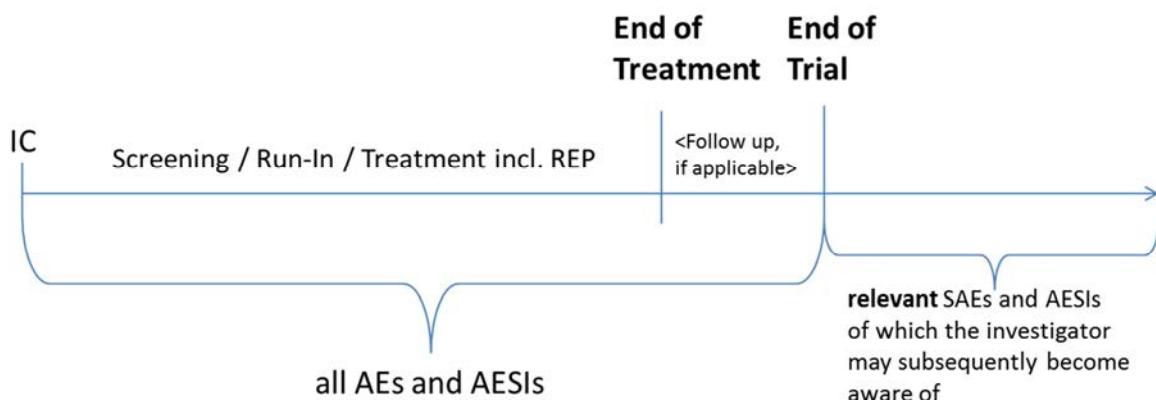


Figure 5.3.7.2: 1 Graphic display of Residual Effect Period (REP)

The REP is defined as 24 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.

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

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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 investigational drug(s) and a Non-investigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AMP).

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

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

Pregnancy

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

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

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

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.7 APPROPRIATENESS OF MEASUREMENTS

The scales being used to assess analgesic efficacy are standard scales used almost universally in controlled clinical trials of analgesic drugs. Since both ibuprofen and caffeine have been marketed (individually) for many years, and the combination is expected to have a safety profile consistent with the individual ingredients, self-reported or observed adverse events will be used to assess safety.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This trial consists of 4 clinic visits. There will also be a follow-up by telephone where the investigator will contact the patient 2-4 Days after visit 4 to determine post treatment safety status (Follow up Visit 5).

Trial visits 1, 2, 3 and 4 should take place in the morning, i.e. ideally be started and concluded between 7:00 a.m. and 11:00 a.m. Patients must adhere to the visit schedule as specified in the [Flow Chart](#).

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 [REDACTED] 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 and run-in period(s)

Screening Period

Screening will be done during the first part of Visit 1. If a patient's eligibility is confirmed, trial treatment will be initiated at the same visit. 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 Screening Period). 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(s)

At Visit 1 (Day 1 post randomization) the first dose of trial medication should be administered at the site by the patient. On Days 1, 2, 3, 4, 5 and the morning of day 6, trial medication should be taken by the patient. The last dose of study drug taken on the morning of Day 6, 1-3 hours before clinic Visit 4 starts. At Visit 1, all procedures indicated in the “Screening Period” column of the [Flow Chart](#) should be performed before the first administration of the trial medication. Procedures indicated in the [Flow Chart](#) as “Treatment period” column should be performed afterwards at time points as indicated.

The trial medication should be dispensed and administered after randomization without delay. The time of the first administration of trial medication should be recorded in the patient’s diary and transcribed into the e-CRF.

The patient should be instructed

- to perform home assessments (███████████ at time points indicated in the [Flow Chart](#))
- to refrain from using rescue medication before the assessments at Visit 2 if possible. If this turns out not to be possible, another supply of rescue medication might be dispensed at another clinic visit
- to record intake of rescue medication (date, time and dose) in the patient’s diary
- to take the trial medication TID every 6-8 hours
- to record the time of all administrations of the trial medication in the patient’s diary
- to bring the diary as well as all unused trial and rescue medication and packaging at each visit.

6.2.3 Follow Up Period and Trial Completion

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.

Patient who want to discontinue the trial treatment prematurely should be asked to have Visit

4 (End of Treatment) in the morning after the last application of the trial medication and to have the telephone follow up Visit 5 at least 48 hours after that last application.

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 3-arm parallel group study to investigate the efficacy and safety of a fixed dose combination of 400 mg ibuprofen and 100 mg caffeine compared to ibuprofen 400 mg and placebo in patients with acute lower back or neck pain.

The patients will be randomised via IRT in blocks to the treatment groups ibuprofen + caffeine, ibuprofen and placebo in a 2:2:1 ratio. Treatment allocation will be stratified by country and the site with the worst pain (wp-site); the wp-site is classified after the POM assessments on a 0-10-point NRS, following the 5 standard procedures, before application at Visit 1 at that site, where the worst pain is identified, and the corresponding POM is then denoted as POM_{WP}. Post-dose POM_{WP} assessments 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 country (Germany or Russia), wp-site (back or neck) and disease severity as covariates.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary objective of this trial is to demonstrate efficacy of the combination ibuprofen 400 mg + caffeine 100 mg, when compared to ibuprofen 400 mg and placebo for the treatment of lower back or neck pain. This will be evaluated by comparing the change in POM_{WP} between baseline (Day 1 morning pre-dosing) and Day 2 morning, 2 hours after drug intake, for the combination treatment vs. the treatment with ibuprofen 400 mg and placebo.

In order to demonstrate efficacy for the complete population (regardless of the stratum (back or neck pain), two-sided tests and a 0.05 level of significance will be used. To this purpose the following statements are hypothesized:

Null hypothesis:

There is no difference in 'Change in POM_{WP} between baseline and Day 2 morning, 2 hours after drug intake' between patients treated with the combination ibuprofen + caffeine and the patients treated with ibuprofen or placebo.

Alternative hypothesis:

There is a difference in 'Change in POM_{WP} between baseline and Day 2 morning, 2 hours after drug intake' between patients treated with the combination ibuprofen + caffeine and the patients treated with ibuprofen and patients treated with placebo.

The set of hypotheses can be written as:

$$H_0: H_{0,1}: \mu_{ibu+caf} = \mu_{ibu} \quad \text{or} \quad H_{0,2}: \mu_{ibu+caf} = \mu_{placebo}$$

versus

$$H_1: H_{1,1}: \mu_{ibu+caf} \neq \mu_{ibu} \quad \text{and} \quad H_{1,2}: \mu_{ibu+caf} \neq \mu_{placebo}$$

, where $\mu_{ibu+caf}$, μ_{ibu} and $\mu_{placebo}$ is the adjusted (for country and wp-site effect, and baseline POM_{WP}) mean change in POM_{WP} between baseline and the morning of Day 2, 2 hours after drug intake, for patients treated with the combination ibuprofen + caffeine, ibuprofen and placebo, respectively.

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

In case H_0 can be rejected for the complete population, the same hypothesis will be tested with respect to the strata back and neck pain using the Hochberg procedure [[P05-11198](#)]:

Step 1:

In case all p-values (obtained without multiplicity adjustments) for the 4 treatment comparisons (2 comparisons per stratum) are below 0.05, superiority of the combination ibuprofen + caffeine versus ibuprofen and placebo can be concluded for both strata, otherwise the following procedure will be performed:

Step 2:

In case there is a stratum with both p-values for the 2 comparisons below alpha/2 = 0.025, superiority of the combination ibuprofen + caffeine versus ibuprofen and placebo can be concluded for the respective stratum, otherwise superiority cannot be concluded for any stratum.

The key secondary endpoints will be analysed for the total population hierarchically (POM_{WP}AUC_{72h} first) in a confirmatory way only, when statistical significance with the total population was achieved for the primary endpoint. Analysis of the key-secondary endpoints for the strata back and neck pain will be descriptive in nature.

All other secondary endpoints 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 took 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 for POM_{WP} at Visit 1 before drug intake and at least one POM_{WP} value at post-treatment assessment times Visit 1 (Day 1 morning, 2 hours after drug intake) and Visit 2 (Day 2, morning, 2 hour after drug intake), will constitute the full analysis set.

Per protocol set (PPS): All patients included in FAS, who revealed no important protocol violations. Important protocol violations, e.g. protocol deviations affecting the results of the primary endpoint, will be defined during blinded report planning meetings and before database lock. All specifications on important protocol violations will be provided in the Trial

Statistical Analysis Plan (TSAP).

7.3.1 Primary endpoint analyses

The primary endpoint ‘Change in POM_{WP} between baseline (Visit 1 pre-dosing) and Day 2 morning, 2 hours after drug intake’ 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, 2 hours after drug intake) and T2 = Visit 2 (Day 2 morning, 2 hours after drug intake).

The statistical model will be applied to the analysis of change from baseline (T0 = Visit 1 morning, before drug intake) in POM_{WP} at times T1 and T2. The statistical model will include the fixed, categorical effects of treatment, country, wp-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, in a first step the ‘singular’ option in the model statement of PROC MIXED may be adjusted to singular =1E-10 (or 1E-9) instead of the default of approximately 1E-12. In case convergence still fails, other covariance structures will be employed following the order ANTE(1), ARH(1) and AR(1).

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom [[R11-1488](#)].

Differences between the treatment group effects (ibuprofen + caffeine vs. ibuprofen and ibuprofen + caffeine vs. placebo with regard to the change in POM_{WP} between T0 and T2, calculated as ‘POM_{WP} at time T0 - POM_{WP} at time T2’ ([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](#).



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_{72h} and POM_{WP}AUC_{120h} will be analysed using an analysis of covariance (ANCOVA) including treatment, country and wp-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 change in PA between baseline and Day 2 morning will be analysed analogously to the primary endpoint using all available longitudinal PA observations at the assessment times T1 = Visit 1 (Day 1 morning, 2 hours after drug intake) and T2 = Visit 2 (Day 2 morning, 2 hours after drug intake). The statistical model will be applied to the analysis of change from baseline (T0 = Visit 1 morning pre-dosing) in PA at times T1 and T2.

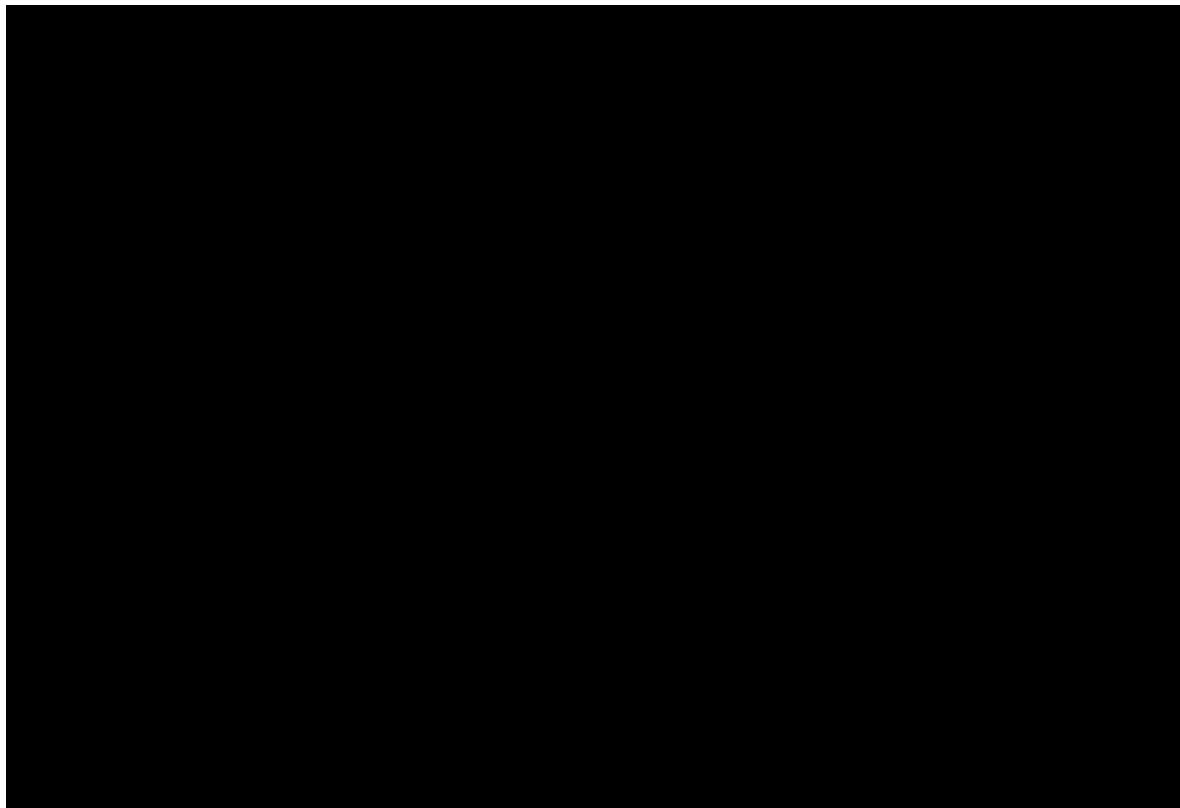
For the multinomial endpoint ‘Global assessment of efficacy by the patient at the end of treatment (Day 6 morning)’ an ordinal logistic regression model adjusting for the categorical variables country and wp-site (back/neck) will be used. The likelihood-ratio test will be used to test for treatment differences. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the treatment effect, comparing all treatments to ibuprofen + caffeine as the reference treatment.

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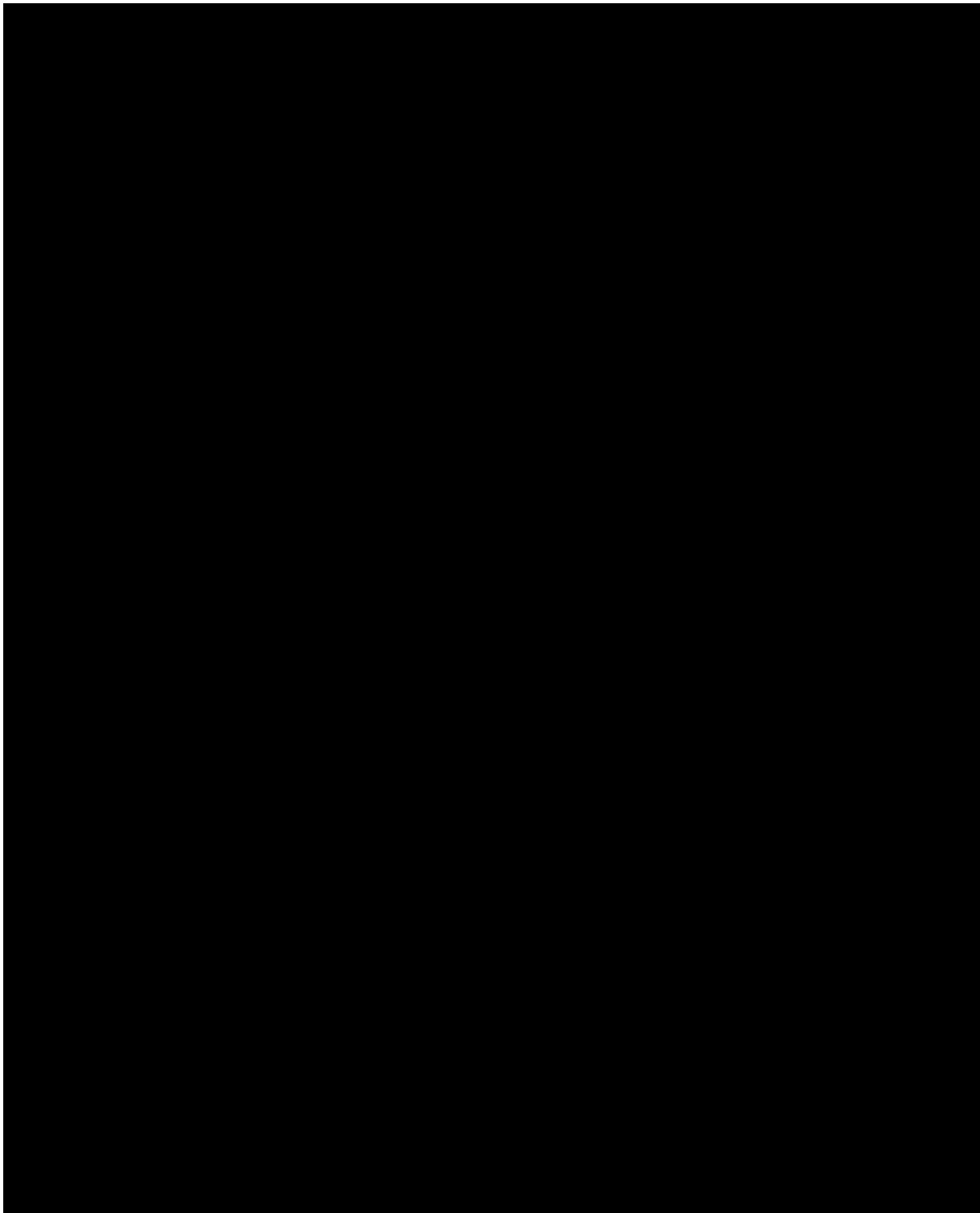
The number of patients with a decrease in POM_{WP} of at least 30% from baseline until Day 2 morning, 2 hours after drug intake, will be analysed by a logistic regression model, adjusting for the categorical covariates country and wp-site (back/neck). The likelihood-ratio test will be used to test for 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 ibuprofen + caffeine as the reference treatment.

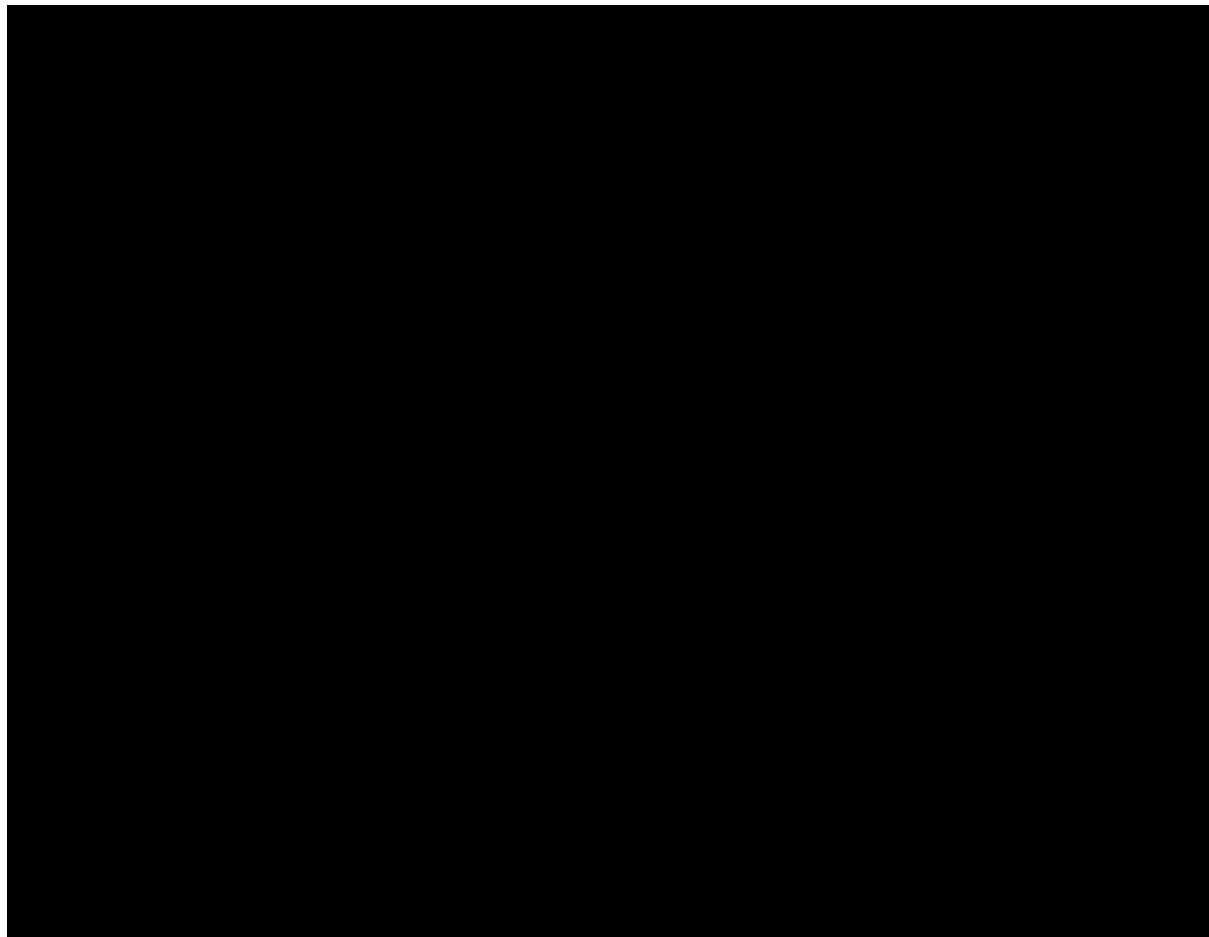
The number of patients with a decrease in POM_{WP} of at least 50% from baseline until Day 2 morning, 2 hours after drug intake, will be analysed correspondingly.

For the time to the first meaningful POM_{WP} relief, a Kaplan-Meier analysis will be performed and the log-rank test stratifying for the categorical variables 'country' and 'wp-site' will be used to test the difference between treatment groups. The time intervals '0 - ≤10 min', '>10 - ≤20 min', '>20 - ≤30 min', '>30 - ≤60 min', '>60 - ≤120 min' and '> 120 min' will be displayed.



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7.3.4 Safety analyses

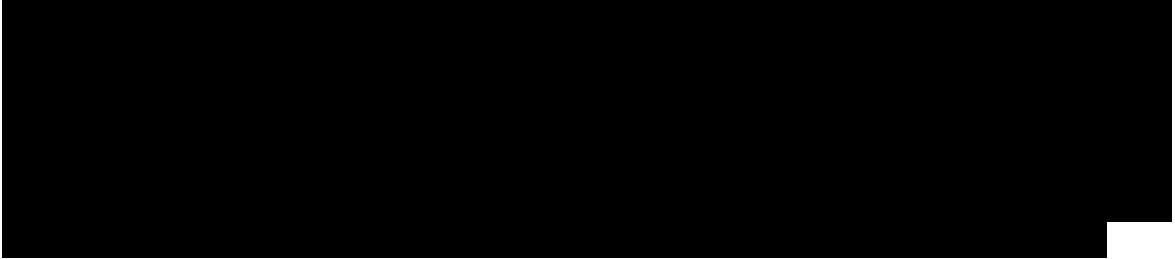
Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and 24 hours following the day of the last dose of trial medication will 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 24 hours following the day of last administration of study drug. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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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).



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.

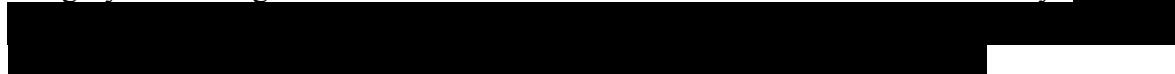
For missing baseline data, no imputation will be implemented.

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

For the calculation of $POM_{WP}AUC_{72h}$ and $POM_{WP}AUC_{120h}$, the following imputation rules for missing POM_{WP} assessments will be applied:

One or more missing assessments in between assessments will be imputed using the planned assessment time(s) and a linear interpolation of the last available assessment before (including baseline, if applicable) and the first available assessment after the missing assessment. If there is no evaluable assessment after the planned time of the missing assessment, planned assessment time(s) and LOCF will be used to impute the POM_{WP} value.

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 patient assessments of efficacy [redacted] resulting from early discontinuation that was clearly unconnected to treatment will be not imputed.

7.6 RANDOMISATION

Patients will be randomised in blocks to the double-blind treatment arms ibuprofen + caffeine, ibuprofen and placebo in a ratio 2:2:1. The randomization allocation will be stratified by country (Russia, Germany) and the wp-site (back/neck).

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 CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy variable 'Change in POM_{WP} between baseline and Day 2 morning, 2 hours after drug intake', which reflects a pain relief on a 0-10 NRS about 24 hours after baseline.

In a previous study investigating diclofenac in comparison to placebo in patients with acute neck pain on a 0-100 mm VAS, 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].

In a previous study investigating the effects of one tablet of ibuprofen + caffeine, ibuprofen, caffeine or placebo, respectively, in patients with post-operative dental pain [c02330821], a standardized difference between the combination and ibuprofen of 0.4 was achieved.

The sample size for this study is based on an anticipated treatment difference of 1.2 on a 0-10NRS and a common standard deviation of 3, yielding a standardized treatment difference of 0.4 concerning the primary endpoint. The allocation ratio to the treatment groups ibuprofen + caffeine, ibuprofen and placebo is planned to be 2:2:1.

Since the strata concerning wp-site (back / neck) will be analysed separately following the Hochberg procedure, the calculation of the sample size will be based on a 0.05 two-sided significance level in order to reject the null hypothesis for both strata.

A sample size of 300 patients per stratum concerning wp-site (back / neck) (120 patients with ibuprofen + caffeine, ibuprofen, respectively and 60 patients with placebo will have 86% power to detect a difference of 1.2 on a 0-10 NRS for the primary endpoint between treatment effects of ibuprofen + caffeine versus ibuprofen (2:2 allocation ratio) and 71% power to detect the same difference between ibuprofen + caffeine and placebo (2:1 allocation ratio), assuming a common standard deviation of 3 and using a 0.05 two-sided significance level. This results in a total sample size of 600 evaluable patients.

With the scenario above, the power for the test of H_0 for the total population will be about 99% for the comparison of ibuprofen + caffeine versus ibuprofen (2:2 allocation ratio) and 94% for the comparison of ibuprofen + caffeine versus placebo (2:1 allocation ratio).

With a level of significance of 0.025 (in case Step 2 of the Hochberg procedure is applicable) and a sample size of 120 in each of the active treatment groups in a respective stratum, the power to detect such treatment difference between the active treatment groups will be 79%.

The sample size of 300 patients per stratum will reach statistical significance in the 2:2 comparison (ibuprofen + caffeine versus ibuprofen), when the observed treatment

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difference is at least 0.76, and in the 2:1 comparison (ibuprofen + caffeine versus placebo), when the observed treatment difference is at least 0.93 (with a 0.05 two-sided significance level and a standard deviation of 3).

In order to provide at least 80% power (on a 0.05 two-sided significance level) for strata analyses concerning the wp-site (back/neck) in the 2:2 comparison (ibuprofen + caffeine versus ibuprofen), a total of 200 patients (ca 42%) of the totally planned 480 evaluable patients in the two active-treatment groups should qualify as either back or neck patients, respectively.

With a level of significance of 0.025 (in case Step 2 of the Hochberg procedure is applicable) and a sample size of 100 in each of the active treatment groups in a respective stratum, the power to detect such treatment difference between the active treatment groups will be 71%.

In total, about 650 patients will be randomised to ensure that 600 patients in the total population are evaluable for the primary endpoint; as soon as 600 patients in total are evaluable for the primary analysis, further recruitment of patients will be stopped.

To ensure that each stratum “back pain” or “neck pain” is represented by at least 42% of the randomised patients, randomisation into a respective stratum will be capped as soon as 58% (about 380 patients) of the total trial population have been randomised to the respective stratum.

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

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and the EU regulation 536/2014

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 Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

Prior to 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.”

The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent

form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

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

Case Report Forms (CRF) 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

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

Trial site(s):

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers. Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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 IRB/IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/135/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial (“Last Patient Out”).

The “**Last Patient Drug Discontinuation**” (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

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

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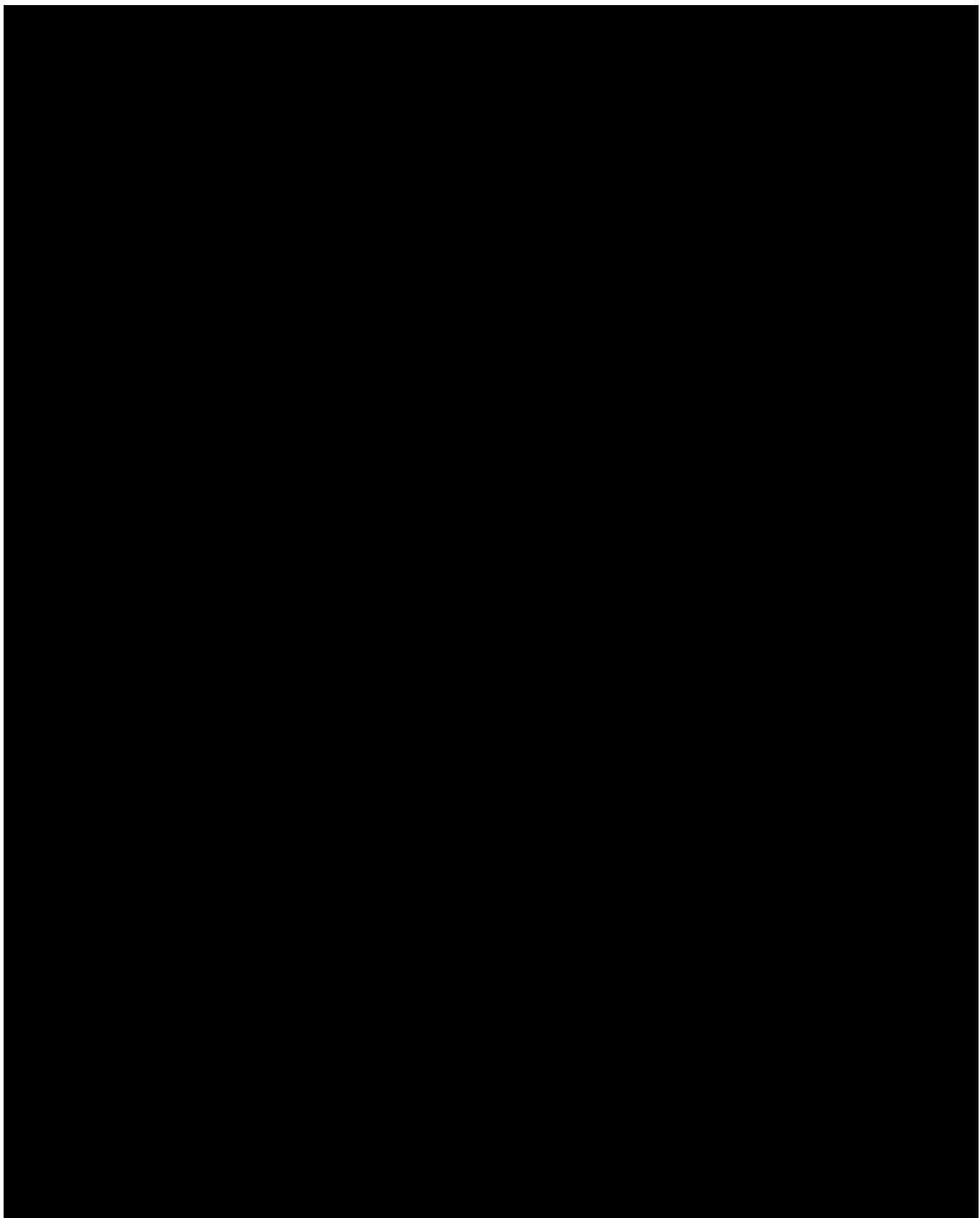
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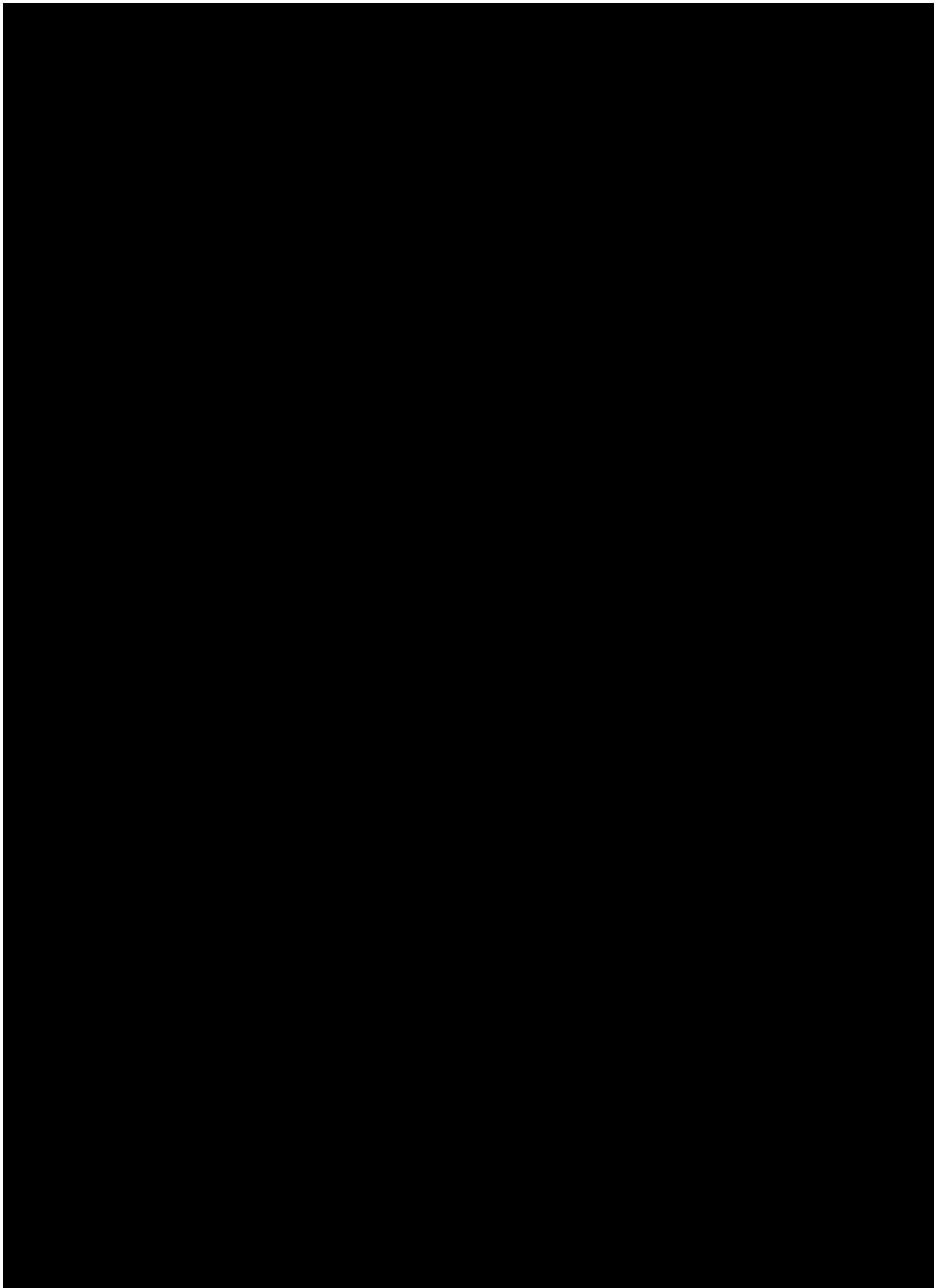
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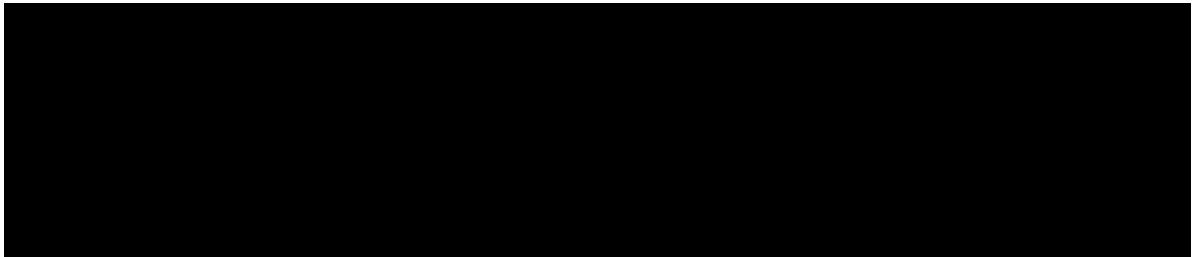
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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment	1
Date of CTP revision	05-AUGUST-2016
EudraCT number	2016-000902-12
BI Trial number	1335.5
BI Investigational Product(s)	Ibuprofen + Caffeine
Title of protocol	A randomized, placebo- and active-controlled multi-country, multi-centre parallel group study to evaluate the efficacy and safety of a fixed dose combination of 400 mg ibuprofen and 100 mg caffeine compared to ibuprofen 400 mg and placebo in patients with acute lower 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	X
Section to be changed	Title Page and Header
Description of change	Version Number and Final Date.
Rationale for change	The protocol was revised because approval workflow had been initiated instead of an e-signature workflow. Content was not changed



APPROVAL / SIGNATURE PAGE

Document Number: c08887804

Technical Version Number: 2.0

Document Name: clinical-trial-protocol

Title: A randomized, placebo- and active-controlled multi-country, multi-centre parallel group study to evaluate the efficacy and safety of a fixed dose combination of 400 mg ibuprofen and 100 mg caffeine compared to ibuprofen 400 mg and placebo in patients with acute lower back or neck pain

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area	[REDACTED]	05 Aug 2016 15:11 CEST
Author-Team Member Medicine	[REDACTED]	07 Aug 2016 17:39 CEST
Approval-Trial Clinical Monitor	[REDACTED]	07 Aug 2016 22:05 CEST
Author-Statistician	[REDACTED]	08 Aug 2016 10:55 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed