STATISTICAL ANALYSIS PLAN
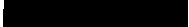
1335.5

A RANDOMISED, 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

AUTHOR:

VERSION NUMBER AND DATE: VERSION 1.0, 29AUG2017

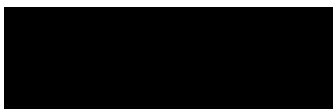Document: Boehringer Ingelheim_1335.5_SAP_V1_0
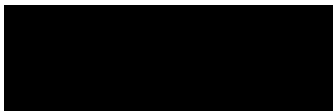Author: Version Number: 1.0
                                                      Version Date: 29AUG2017

Template No: CS_TP_BS016 Revision 4   Reference: CS_WI_BS005
Effective Date: 01Apr2016

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE·

Statistical analysis plan V1.0 (Dated 29AUG2017) for Protocol 1335.5.

	Name	Signature	Date (DDMMMYYYY)
Author:	▮▮▮▮▮▮	**Refer to electronic signature on separate page**	
Position:	Statistical Team▮		
Company:	▮▮▮▮▮		

Upon review of this document, the undersigned approves this version of the statistical analysis plan, authorising that the content is acceptable for the reporting of this study.

	Name	Signature	Date (DDMMMYYYY)
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Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
1.0	29AUG2017	███████	Not applicable – First version
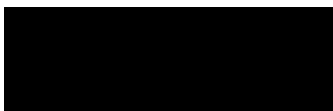
TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 1335.5. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.0, dated 05 August 2016.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

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

2.2. SECONDARY OBJECTIVE

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

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase III, multi-centre, double-blind, parallel-group study, with a total of 650 research patients (with the aim to have 600 evaluable patients) randomised in a 2:2:1 ratio to three treatment groups as described in Table 1: Treatment Groups, below:

Table 1: Treatment Groups

Presentation Order	Treatment Group	Number of Patients	Interventions
1	Placebo	~130	Placebo tablet
2	Ibuprofen	~260	400 mg ibuprofen tablet
3	Ibuprofen + caffeine	~260	400 mg ibuprofen and 100 mg caffeine tablet

3.2. SCHEDULE OF EVENT

Schedule of events can be found in Section 6.2: Details of Trial Procedures at Selected Visits as well as in the flow chart of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

No changes were made to the planned analysis.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

4.2. FINAL ANALYSIS

The unblinded final, planned analysis identified in this SAP and supporting TLF shells will be performed by ▮▮▮▮▮▮ Biostatistics. The final analysis is planned following:

• Boehringer Ingelheim's authorisation of:

  o Final version of the SAP.
  o Relevant set of TLF shells.
  o Final analysis sets and reason(s) for exclusion/important protocol violations.

• Final database lock (DBL).

• Routine study unblinding.

• Identification of treatment deviations.

The final analysis is planned when all patients have completed study participation.

The final analysis will be performed on a clean database snapshot:

• All outstanding data issues and queries resolved, as far as feasible and as indicated in the authorised data issues log.

• All unresolved data issues documented in the authorised data handling report (DHR) from data management (DM).

• All coding of medical history (MH), concomitant medication (CM) and adverse events (AEs) completed.

- Serious adverse event (SAE) and interactive web response system (IWRS) reconciliation completed by data management.

5. ANALYSIS SETS AND IMPORTANT PROTOCOL VIOLATIONS (IPVS)

Boehringer Ingelheim's authorisation of the analysis set assignment, identification for reasons for exclusion from analysis sets in addition to important protocol violations identified during the clinical conduct of study is required prior to database lock and the routine unblinding of the study and final analysis.

5.1. ANALYSIS SETS

There are three analysis sets defined as follows for this study:

- Treated set (TS):
  - o All randomised patients;
  - o Who took at least one dose of the trial medication.
    - Patients having received the wrong treatment will be analysed within the planned (randomised) treatment group in the efficacy analysis and within the actual (as treated) treatment group in the safety analysis.
    - Patients who are incorrectly randomised into the stratum not containing their POM_{WP} will be included in TS as randomised, but will be allotted to the stratum with the POM_{WP}.

- Full analysis set (FAS):
  - o All patients included in the TS;
  - o Who provided a baseline value for POM_{WP} at Visit 1 (Day 1) before drug intake;
  - o Provided at least one post-baseline POM_{WP} assessment at the following time points:
    - Visit 1 (Day 1, 120 minutes after drug intake).
    - Visit 2 (Day 2, 120 minutes after drug intake).

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Additionally a limited number of presentations will be based on the following two patient sets:

- Enrolled patients:
  - o All patients who were screened in this study (provided informed consent).

- ■ ███████████

- ■ ██

These patient/analysis sets will be utilised in the domain-specific analysis as detailed in Table 2: Analysis Set Relevant to Domain-specific Analysis, below:

Table 2: Analysis Set Relevant to Domain-specific Analysis

Domain	Analysis Set
Disposition	Enrolled patients
████████	██████████
IPVs	TS (as randomised)
Demographics and other baseline characteristics	
Concomitant therapies	
Treatment compliance	
Efficacy analysis: primary endpoints	FAS (primary)
	██████████
Efficacy analysis: secondary ████████ endpoints	TS (as randomised)
Safety analysis	TS (as treated)

5.2.   IMPORTANT PROTOCOL VIOLATIONS (IPVs)

The IPVs defined for this study are provided in Table 3: Detailed List of IPVs, below. Based on the response to the programmatically identified in the last column of Table 3, the IPVs will be identified as follows:

- Yes:
  - o Programmed check by the biostatistics team to identify the patients with these IPVs.

- No:
  - o IPVs identified by the clinical team on an ongoing basis.
  - o These manual IPVs will be documented in Clinical Trial Management System (CTMS) as a protocol violation.
  - o These manual IPVs will be transferred to the biostatistics team for incorporation in the analysis.

- Yes/No:
  - o IPVs identified by the medical/clinical team on an ongoing basis.

o The biostatistics team can provide relevant outputs to assist in the identification of these IPVs, in which case the noted IPVs will be noted on the provided outputs to be considered during the analysis.

Table 3: Detailed List of IPVs

Category/ Code	IPV Description	Comment/Example	Efficacy/ Safety (E/S)	Programmatically Identified
A	Entrance criteria not met			
A.1	Inclusion criteria not met			
A1.01	Diagnosis of acute back pain or neck pain < 24 hours or ≥ 21 days	IN2	E	Yes/No
A1.02	Any baseline POM procedure missing or not done	IN3	E	Yes/No
A1.03	POM < 5 for all 5 baseline procedures	IN3	E	Yes
A1.04	Sensitivity to algometric pressure on the painful trigger point > 25 N/cm²	IN4	E	Yes
A.2	Exclusion criteria met			
A2.01	History of 3 or more episodes of back or neck pain in the last 6 months excluding the current episode.	EX1	E	Yes/No
A2.02	Pain at rest ≥ 9	EX2/EX3	E	Yes
A2.03	Patient with chronic back or neck pain as defined as pain for 3 weeks or longer.	EX4	E	Yes/No
A2.04	Back or neck pain that is attributable to any identifiable cause	EX5	E	Yes/No
A2.05	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	EX6	E	Yes/No
A2.06	Surgery due to back or neck pain or rehabilitation due to back or neck pain in the last 12 months	EX7	E	No
A2.07	Prior use within the last 3 days before Visit 1 or concomitant use of any anti-inflammatory drugs, heparinoids, muscle relaxants or analgesics (see CTP for exceptions)	EX8	E, S	Yes/No

Category/ Code	IPV Description	Comment/Example	Efficacy/ Safety (E/S)	Programmatically Identified
A2.08	Spinal injections or long-acting glucocorticoids not discontinued in due time	EX9	E	No
A2.09	Known severe hepatocellular insufficiency, severe renal insufficiency or Gilbert's syndrome	EX10	S	No
A2.10	Use of CNS or other psychotropic drugs, or any nutritional supplement known to have psychotropic effects	EX11	S	No
A2.11	Any other medical condition that would interfere with efficacy and safety assessments	EX12	E, S	No
A2.12	Known intolerance or hypersensitivity to the active ingredients or any excipient(s)	EX13	S	No
A2.13	Patient not able to understand and comply with trial requirements based on investigators judgment	EX14	E, S	Yes
A2.14	Major surgery performed within 12 weeks prior to randomization or planned within timeframe of this study	EX15	E, S	No
A2.15	Patient must or wishes to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	EX16	E, S	Yes
A2.16	Previous enrolment in this trial	EX17	E, S	No
A2.17	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)	EX18	E, S	No
A2.18	Habituation to analgesic drugs or caffeine (see CTP for further specification)	EX19	E, S	No

Category/ Code	IPV Description	Comment/Example	Efficacy/ Safety (E/S)	Programmatically Identified
A2.19	History of allergic reaction (see CTP for further specification)	EX20	S	No
A2.20	Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable study subject or unlikely to complete the trial	EX21	E, S	No
A2.21	Women who are pregnant, nursing, or who plan to become pregnant while in the trial	EX22	S	Yes
A2.22	Prior use of any type of analgesic or NSAID within 5 half-lives of that drug before initial dosing in the trial	EX23	E, S	No
A2.23	Presence or history (within 2 years of enrolment) of bleeding disorder or peptic ulcer disease	EX24	S	No
A2.24	Has a clinically significant abnormal electrocardiogram (ECG) at screening as determined by the investigator	EX25	S	Yes
A2.25	Has known impaired liver function (see CTP for further specification)	EX26	S	No
A2.26	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	EX27		No
B	Informed consent			
B1	Informed consent not given	Date of informed consent missing	E, S	Yes
B2	Informed consent given too late	Date of informed consent not obtained prior to any study related procedure	S	Yes
C	Trial medication and randomisation			

Category/ Code	IPV Description	Comment/Example	Efficacy/ Safety (E/S)	Programmatically Identified
C1	Incorrect trial medication taken	Less or more than 4 tablets taken until Visit 2	E	Yes/No
C2	Randomisation order not followed	Patient received trial medication from medication kit not assigned to them. If patients actually receive the correct medication, despite receiving the wrong kit, they will not be excluded from the PPS.	E, S	Yes/No
C3	Medication code broken	Medication code broken inappropriately	E	No
C4	Incorrect stratum (back/neck) selected based on POMWP.	If a patient is not randomised into the stratum containing the POMWP.	E	Yes
D	Concomitant medication			
D1	Medications not stable at least 2 weeks before randomisation visit	Antidepressants or antipsychotics not stable from at least 2 weeks before randomisation	E	Yes
D2	Prohibited medication use during the treatment period	Prohibited use of concomitant treatments as described in CTP section 4.2.2.1	E	Yes/No
D3	Improper use of rescue medication	More than 4 paracetamol tablets (of 500mg) taken on treatment day 1	E, S	Yes/No
F	Incorrect timing			
F1	Incorrect timing of visits			

Category/ Code	IPV Description	Comment/Example	Efficacy/ Safety (E/S)	Programmatically Identified
F1.1	V2 completed outside of time window	Visit 2 not performed on day 2 between 7 and 12 am	E	Yes
F1.2	Follow-up period too short	Follow-up visit completed < 24 hours after the day of the last dose of trial medication	S	Yes
F2	Incorrect timing of measurements			
F2.1	POM assessment not between 115 minutes and 125 minutes after application of trial medication	IPV only on day of primary endpoint	E	Yes
G	Other			
G1	Other PV affecting efficacy and possibly safety			
G1.1	Assessment of POM by untrained staff		E, S	No
G1.2	Assessment of POM on screening, randomisation and day 2 not done by the same person (within a patient)		E	Yes
G2	Other PV affecting safety only			
G2.1	Pregnancy test not performed	Missing pregnancy test result for any women of childbearing potential	S	Yes
G3	Significant GCP non-compliance	It should be described carefully in the DBL meeting minutes, which analyses are affected	S	No

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND RELATIVE DAY

Relative day is calculated from the reference start date, and will be used to show start/stop day of assessments and events.
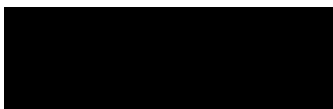
Reference start date is defined as date/time of first administration of trial medication. The first occurrence of either Ibuprofen + caffeine or Ibuprofen or placebo tablet will be considered for all patients.

- If the date/time of the assessment/event is on or after the reference start date then:
  o Relative Day = (Date/time of assessment/event – Reference start date/time) + 1.
- If the date/time of the assessment/event is prior to the reference start date then:
  o Relative Day = (Date/time of assessment/event – Reference start date/time).

Unless otherwise specified, if the assessment/event date is partial or missing, relative day, and any corresponding durations will not be calculated and will be presented as missing in the listings. For further details regarding the partial date conventions, refer to APPENDIX 1: Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing assessment prior to the first administration of trial medication (reference start date/time). In the case where the last non-missing assessment and the reference start date/time coincide, that assessment will be considered as occurring prior to the start of administration of the trial medication and will be used as the baseline assessment.

However, AEs and medications commencing on the reference start date will be considered post-baseline if there is only a date available, e.g. as treatment-emergent AEs or concomitant medications. If a date/time is available for AEs and CMs then the events/medication will be assigned accordingly.

For assessments with time available, baseline is calculated as the last non-missing assessment prior to the first start date and time of trial medication. Time of assessment relative to time of first administration of the trial medication will be used to differentiate between pre- and post-administration assessments.

6.3. RETESTS, UNSCHEDULED VISITS

In general, for by-visit summaries, data recorded at the scheduled visits will be presented. There are no unscheduled visits available on the eCRF (e.g. between scheduled visits) for this study and subsequently unscheduled data is not collected.

6.4. WINDOWING CONVENTIONS AND STUDY PERIODS

Time windows for visits are shown in the flow chart in the clinical trial protocol. Visits 1 and 2 must be carried out on the specified days, for visit 3 and 4 there is a time window of ± 1 days.

Endpoint variables captured outside the defined visit window will be flagged in the IPVs.

If a single scheduled visit is completed outside of the visit window, as defined in the protocol, that visit will be assigned to the scheduled visit. For example, if a patient completes a visit in the afternoon of day 2, the visit would be assigned to visit number 2.

If more than one consecutive scheduled visits are missed, and a single visit completed to compensate for the missed visits, the completed visit will be assigned to the closest scheduled visit among those missed visits.

The study periods are defined in Table 4: Study Periods, below.

Table 4: Study Periods

Study Period	Start of Period	End of Period
Screening (S)	Informed consent obtained	First intake of trial medication
On-treatment (OT)	First intake of trial medication	Day and time of last administration of trial medication + 24 hours
Post-treatment (PST)	Day and time last administration of trial medication + 24 hours	Trial termination date
Post-study (PS)	Trial termination date	Post-trial termination date

6.5. GENERAL STATISTICAL TESTS AND CALCULATIONS

This section provides general details on the descriptive statistical analysis. The details regarding statistical testing is described in the domain-specific analysis sections.

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

Unless otherwise specified, the default summary statistics are:

- Quantitative variables:
    o Number of patients with non-missing values in each category.
    o Mean.
    o Standard violation (SD).
    o Minimum.
    o Q1 (lower quartile).
    o Median.
    o Q3 (upper quartile).
    o Maximum.

- Qualitative variables:
    o Number of patients with non-missing values in each category.
    o The percentage of patients (rounded to one decimal place) in each category (%) presented relative the total number of patients in the respective treatment group.
    o For categorical and ordinal data, all possible categories will be displayed.
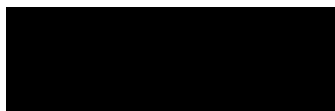
The category missing will be displayed only if there are actually missing values.

All values will be rounded using the SAS® function ROUND as the last step prior to presentation.

If the original data has N decimal places (as derived from the raw data), then the summary statistics for the quantitative data will contain the following number of decimal places (with a maximum of 4 decimal places):

• Minimum and maximum: N.

• Mean and median: (N+1).

• Standard deviation: (N + 2).

All p-values will be presented with 4 decimal places, if less than 0.0001 (after rounding to 4 decimal places) the p-value will be displayed as < 0.0001. Odds ratios and CIs will be presented to 3 decimal places.

Patient data listings will be based on the randomised set.

For all efficacy analysis pertinent to the WP-site and applicable only the FAS, any patient who is incorrectly randomised into the stratum (back/neck) not containing the POMWP will be included in the stratum with the POMWP.

Common Calculations:

• Change in POM_{WP} between T_0 and T_x will be calculated as follows:

   o Change in POM_{WP} = POM_{WP} at T_0 - POM_{WP} at T_x
   o The same calculation will be applied for change in pressure algometry (PA).

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• For quantitative measurements, % change from baseline will be calculated as:

   o % Change from baseline at Visit X = (Change from baseline at visit X/baseline) X 100.

For descriptive analysis, if a result is missing, change from baseline will be presented as missing in the listing; hence no imputation for a missing change from baseline will be performed.

Date/time of first and last trial medication administration:

• First: Chronologically sorting date/time of the trial medication administrations within a patient and selecting the earliest date/time available.

• Last: Chronologically sorting date/time of the trial medication administrations within a patient and selecting the latest date/time available.

6.6. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES TO BE INCLUDED IN ANALYSES

Due to the stratification of randomisation, country and worst procedure site (wp-site) (back/neck) will be analysed as covariates. Additional covariates are detailed in the relevant domain-specific analysis sections.

7.2. MULTI-CENTRE STUDIES

This study will be conducted by multiple investigators at multiple sites in Germany and Russia. Randomisation to treatment groups is stratified by country.

The following research centres are included in this study:

- Germany: All centres starting with ███
- Russia: All centres starting with ██.

7.3. MISSING DATA

For missing baseline data, no imputation will be implemented.

Missing safety data will not be imputed, ██ ██████████

Missing efficacy data will be handled as described in Section 14: Efficacy Analysis, of this analysis plan.

For the handling of missing or partial dates, refer to APPENDIX 1: Partial Date Conventions.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

7.4.1. PRIMARY ENDPOINT

In order to demonstrate efficacy, two-sided tests and a 0.05 level of significance will be used. To this purpose the following is hypothesized:

Null hypotheses:

There is no difference in change in POMwp 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.
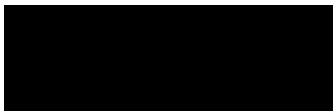
Alternative hypotheses:

There is a difference in Change in POMwp 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 only.

The hypotheses can be written as:

$$H_0: H_{0,1}: \mu_{ibu+caf} = \mu_{ibu} \; OR \; H_{0,2}: \mu_{ibu+caf} = \mu_{placebo}$$

versus

$$H_1: H_{1,1}: \mu_{ibu+caf} \neq \mu_{ibu} \; AND \; H_{1,2}: \mu_{ibu+caf} \neq \mu_{placebo}$$

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

Since both partial hypotheses $H_{0,1}$, and $H_{0,2}$ must 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, the same hypothesis will be tested with respect to the strata back and neck pain using the Hochberg procedure.

Step 1:

In case all p-values (obtained without multiplicity adjustments) for the four treatment comparisons (back: ibuprofen + caffeine vs. ibuprofen and placebo respectively; neck: ibuprofen + caffeine vs. ibuprofen and placebo respectively) are below 0.05, superiority of the combination ibuprofen + caffeine versus ibuprofen and placebo only 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.

7.4.2.   SECONDARY ENDPOINTS

The key secondary endpoints will be analysed for the total population hierarchically (POMWPAUC72h 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.
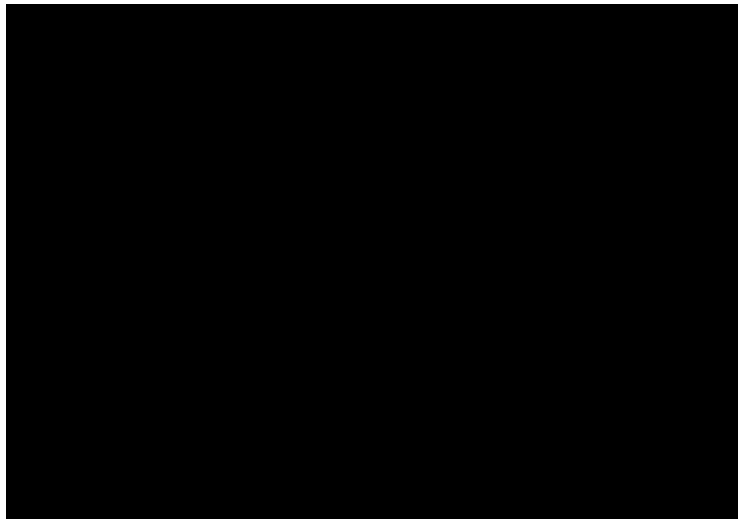
8. OUTPUT PRESENTATIONS

8.1. DATES & TIMES

Depending on data available, dates and times are to take the form yyyy-mm-ddThh:mm. Partial dates will not be imputed and hence displayed as partial in the planned listings. For further details regarding the handling of partial dates and assigning therapies to study periods, refer to APPENDIX 1: Partial Date Conventions.

8.2. SPELLING

English UK spelling will be applied.

Note that verbatim terms, specifications (e.g. the reason a specific assessment was not done) in the TLF shells that contain the suffix (eCRF), contain free text fields which may include spelling mistakes. Verbatim text will be presented in the listings as is and no manual hard-coding corrections of such data will be made.

8.3. PRESENTATION OF TREATMENT GROUPS AND VISITS

Refer to Table 1: Treatment Groups for the details regarding the treatment groups and order of presentation.

Refer to **Error! Reference source not found.** for the details regarding the planned visits and labelling.

9. DISPOSITION AND PREMATURE DISCONTINUATION

All patients who provide informed consent will be accounted for in this study.

Patient disposition and primary reason for premature trial discontinuation, analysis sets (as defined in section 5.1: Analysis sets) and IPVs (as defined in section 5.2: Important Protocol Violations (IPVs)) will be summarised. The reasons for exclusion from analysis set (IPVs) will be reviewed and authorised by Boehringer Ingelheim at the final BDR meeting.

Patient disposition, reasons for non-inclusion and discontinuation, analysis sets and reasons for exclusion as well as IPVs will be listed.

Treatment violations will be identified by using the report provided by Almac and the CTMS report:

9.1. DERIVATIONS

Study completion:

- Completed study Yes: If the patient did not prematurely stop the trial medication is selected on the Termination of Trial Medication eCRF.

- Completed study No: If one of the following is selected:
  - Adverse event:
    - Unexpected worsening of disease under study.
    - Unexpected worsening of other pre-existing disease.
    - Other adverse event.
  - Lack of efficacy.
  - Non-compliant with protocol.
  - Lost to follow-up.
  - Patient refusal to continue taking trial medication.
  - Other.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

No statistical testing will be carried out for demographic or other baseline characteristics.

Demographics and baseline clinical signs of disease will be listed and summarised descriptively by treatment group and total based on the Treated set.

10.1. DERIVATIONS

- Age will be summarised as collected on the eCRF and not rederived.

- Age class (years): Refer to section 7.5: Examination of Subgroups for the relevant age class defined for analysis.

- ██

  - ██

11. HISTORICAL, CONCOMITANT THERAPIES AND BASELINE CONDITIONS

Historical medication as well as medication taken at baseline or during the treatment period will be summarised by World Health Organization-Drug Dictionary (WHO-DD) preferred term (PT), and presented by treatment group and all patients combined.

Patients with more than one finding will be counted only once per preferred term. The table will be presented by preferred term by total descending frequency. Where different preferred terms have the same total frequency, the preferred terms will be sorted alphabetically.

Concomitant analgesic medication taken at baseline or during the treatment period will be summarized separately from both rescue medication and from all other concomitant medication.

Historical and concomitant therapies will be coded using the most recent WHO-DD version. Uncoded terms will be displayed last within the category Uncoded and utilising the verbatim term entered on eCRF as WHO-DD drug name (e.g. Uncoded/Ointment).

Analgesic therapies will be identified through a medical review of all therapies recorded in the database by Boehringer Ingelheim.

Baseline conditions / concomitant diagnoses will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and PT, and presented by treatment group and the total of all subjects

11.1. DERIVATIONS

All therapies will be classified as detailed in Table 5: Therapy Classification, below:

Table 5: Therapy Classification

Historical	Concomitant		Post-treatment
Ending at first intake of trial medication	Between first trial medication and Day 2 morning 2 hours	Starting later than Day 2 morning 2 hours	Starting after last intake of trial medication

Therapies ending before the first administration is classified as historical therapies. Therapies can be both concomitant and post-treatment if taken within both periods as define in Table 5: Therapy Classification, above.

In the therapy listings, analgesic therapies will be indicated by a *.

Partial therapy dates will be imputed as detailed in APPENDIX 1: Partial Date Conventions.

Indication/Specification (eCRF):

- Medical History will be concatenated with the actual medical history verbatim term by merging the medical history number on the Prior and Concomitant Medication eCRF with the medical history number on the Medical History eCRF:

  o Medical history/Medical history verbatim term.

- Adverse event will be concatenated with the actual AE verbatim term by merging the AE number on the Adverse Events/Serious Adverse Event eCRF with the AE number on the Prior and Concomitant Medication eCRF.
  o Adverse event/Adverse event verbatim term.

12. MEDICAL HISTORY

Medical history findings will be summarised by treatment group and total based on the Treated set.

Patients with multiple medical history findings will be counted only once per primary System Organ Class (SOC) and Preferred Term (PT).

The table will be presented by primary SOC by total descending frequency and by PT by total descending frequency within SOC. Where different SOCs or PTs have the same total frequency, the SOCs or PTs will be sorted alphabetically.

Medical history findings will be coded using the most recent MedDRA version. Uncoded terms will be displayed last within the category Uncoded and utilising the verbatim term entered on the Medical History eCRF as PT (for example Uncoded/Soft tummy).

12.1. DERIVATIONS

No imputation of partial or missing dates will be performed and partial dates will be presented as collected on the Medical History eCRF.

Treatment/Specification (eCRF):

- Treatment specification (verbatim term) will be mapped from the Prior and Concomitant Medication eCRF by merging the medical history sequence number on the Medical History eCRF with the medical history sequence number from the Prior and Concomitant Medication eCRF (for example Augmentin).

13. TRIAL MEDICATION EXPOSURE AND COMPLIANCE

Trial medication exposure and trial medication compliance will be summarised overall and per study day by treatment group and total based on the Treated set.

Exposure will be summarised descriptively in terms of the number of tables taken. Furthermore, duration of treatment exposure will be determined for each patient during the randomised treatment period.

Compliance data will be summarised as % compliance both overall as well as at Day 2 morning. Additionally the frequency distribution of number of tables administered overall and per study day will be presented.

Per protocol administration should be one tablet three times daily with intervals of 6 to 8 hours over 5 days (up to Day 6 morning).

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		Version Date:	29AUG2017

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Effective Date: 01Apr2016
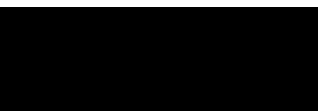
The trial medication administration variables, as presented in the planned TLF shells, will be collected on the Patient Diary and Patient Diary-Last Day eCRFs.

13.1. DERIVATIONS

- Duration of treatment exposure (days):

  o Number of days on treatment = Treatment discontinuation date – treatment date +1.

- Hours since previous tablet = (Current administration date/time - previous administration date/time).

- Hours since first medication intake and Day 2 morning = (Day 2 morning first intake (date/time) – First medication intake (date/time)).

- Day 2, morning compliance to trial medication (%) = $\dfrac{\text{(Number of tablets actually taken)}}{\text{(Number of tablets which should have been taken, Day 2, morning)}}$ x 100

  o Expected number of tablets to be taken by Day 2, morning:
      - If first intake on Day 1 was on or before 12:00, then expected # = 4.
      - If first intake on Day 1 was later than 12:00, then expected # = 3.

- Overall compliance to trial medication (%) = $\dfrac{\text{(Number of tablets actually taken)}}{\text{(Number of tablets which should have been taken)}}$ x 100

  o Expected number of tablets = (Number of days on treatment x 3) - 2

- Compliance (%) classified as:

  o < 80.
  o ≥ 80 to ≤ 120.
  o > 120.

14. EFFICACY ANALYSIS

Efficacy analysis will be presented for patients in the full analysis set and repeated for the per protocol set for the primary efficacy endpoint and for the Treated set for the secondary endpoints.

14.1. PRIMARY EFFICACY ENDPOINT

14.1.1. PRIMARY ENDPOINT AND ANALYSIS OF THE PRIMARY EFFICACY VARIABLE

The primary efficacy variable is change in pain on movement worst procedure (POMwp), between baseline (Day 1 [pre-dose]) and Day 2 morning, 2 hours after trial medication intake (Day 2 [120 min]). The POMwp is assessed on a 0 to 10 numerical rating scale (NRS).

The POMwp is defined as the pain on movement procedure with the highest pain score at baseline.
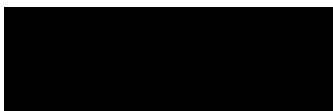
Descriptive statistics overall as well as by relevant subgroups (refer to section 7.5: Examination of Subgroups) and treatment group for the POMwp result as well as the change in POMwp (refer to section 0: Common Calculations for the relevant calculation of change).

Relevant time points for the analysis of the primary endpoint include the following:

- $T_0 = Day\ 1\ (Pre - dose)$ (included as a covariate in the statistical model)

- $T_1 = Day\ 1\ (120\ min)$

- $T_2 = Day\ 2\ (120\ min)$

14.1.2. MISSING DATA

Missing data points will not be imputed. The mixed model repeated measures (MMRM) is the primary analysis method compensating for missing data.

14.1.3. MIXED MODEL REPEATED MEASURES (MMRM)

The primary endpoint will be analysed utilising a restricted maximum likelihood (REML) based repeated measures approach, using the time points as noted in section 14.1.1: Primary Endpoint and Analysis of the Primary Efficacy Variable.

Differences between the treatment group effects (ibuprofen + caffeine vs. ibuprofen and ibuprofen + caffeine vs. placebo) with regard to the change in POMwp between Day 1 (pre-dose) and Day 2 (120 min) will be estimated by reference to the adjusted least square means ($LMS_{ibu+caf} - LSM_{ibu}, LSM_{ibu+caf} - LSM_{placebo}$) and the corresponding 95% confidence intervals (CI). All statistical testing will be performed using a two-sided, alpha = 0.05 level of significance.

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 POMwp and baseline-by-time interaction.

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.

The following model will be fitted:

proc mixed data=<data> method=reml cl covtest;

class treatment country wp_site time patient;

model cfb =   treatment baselinePOMwp country wp_site time treatment*time baselinePOMwp*time / ddfm=KenwardRoger s;

repeated time / type=UN subject=patient;
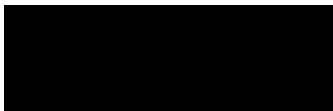
lsmeans treatment*time / diff cl;

run;

where

cfb   = Change in POMwp from baseline

Treatment   = Treatment group (Ibuprofen + caffeine/ibuprofen/placebo).

Country   = Germany/Russia.

Wp_site   = Worst procedure site (back/neck).

Time   = Time point (Day 1 (120min), Day 2 (120min)).
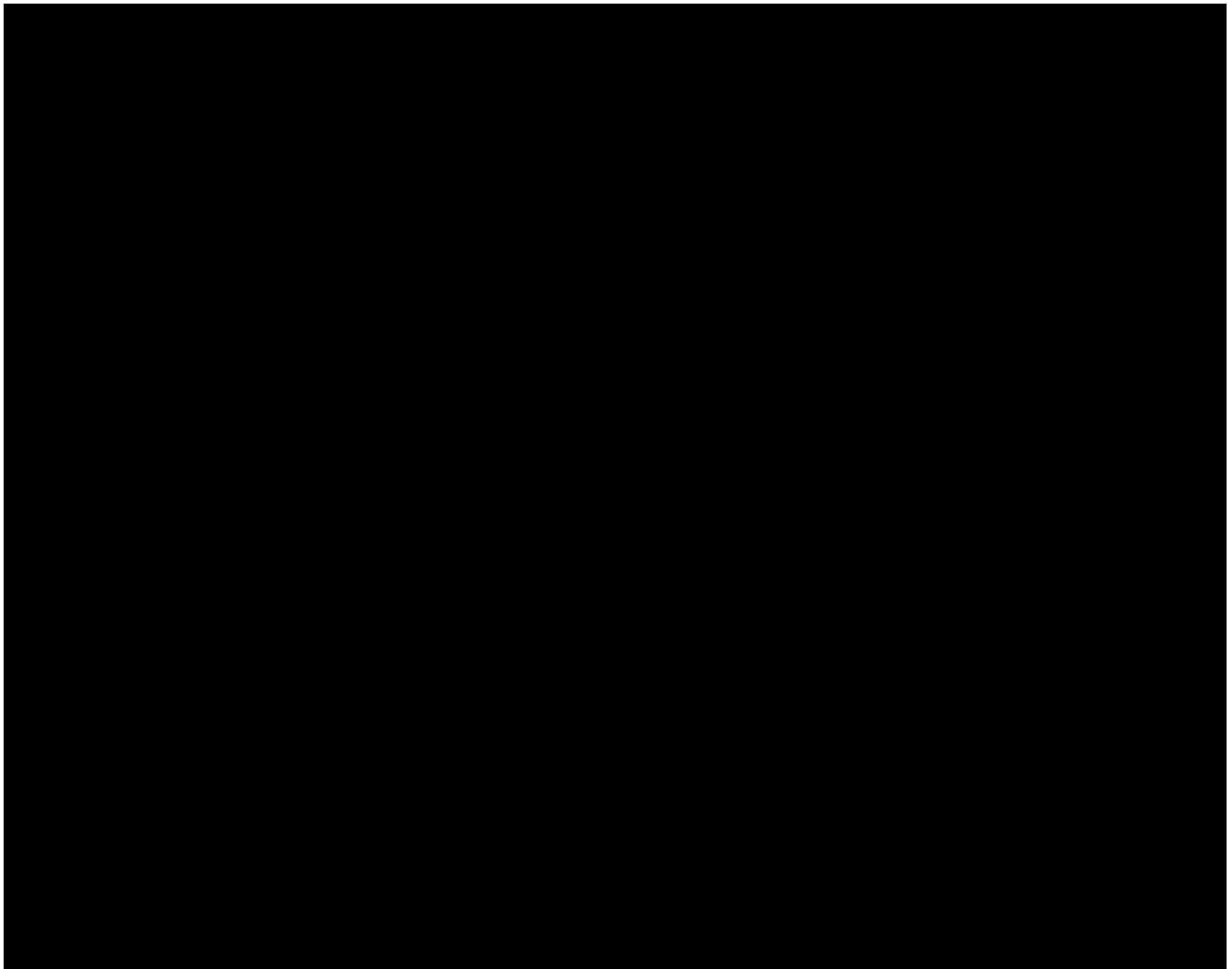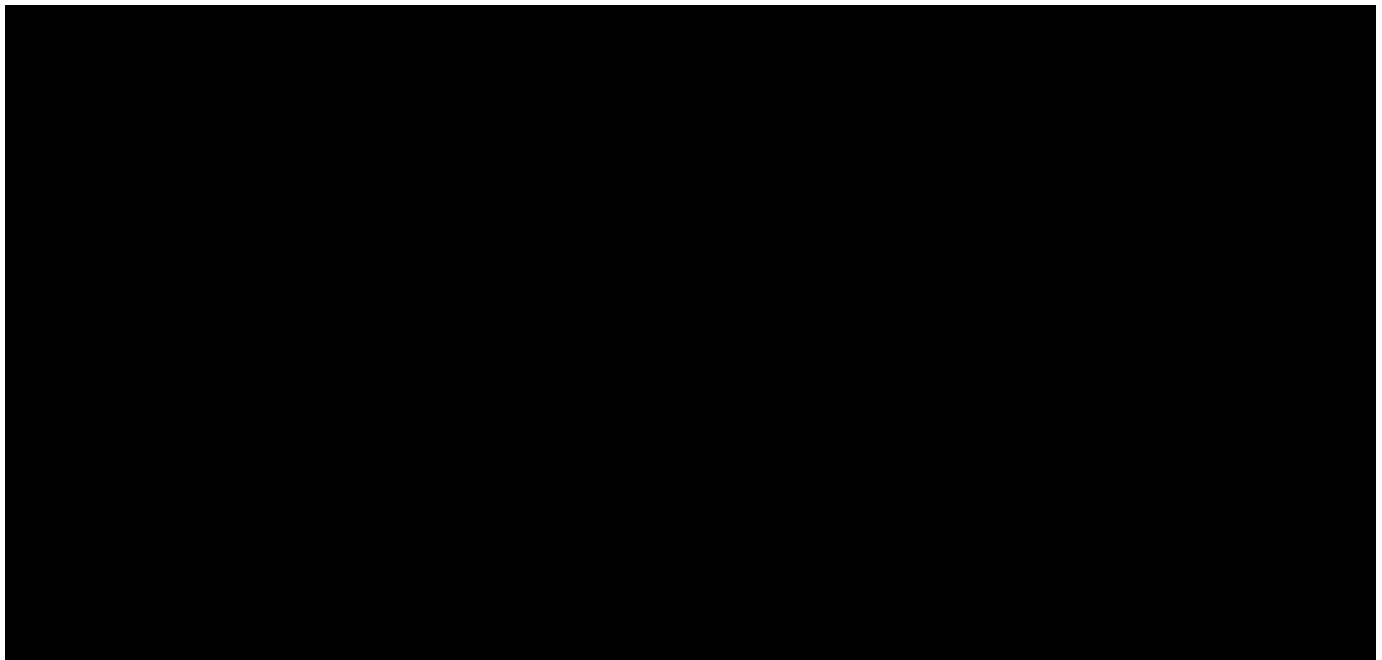
14.2. SECONDARY EFFICACY ENDPOINTS

The secondary efficacy analyses will be performed for the Treated set.

14.2.1. ANALYSIS OF KEY SECONDARY EFFICACY VARIABLES

Descriptive statistics overall as well as by relevant subgroups (refer to section 7.5: Examination of Subgroups) and treatment group will be presented for the relevant key secondary efficacy endpoint. In addition, the key secondary endpoints will be analysed using an analysis of covariance (ANCOVA).

14.2.1.1. Area Under the Curve (AUC) for POMwp between Baseline and the morning of Day 4 (POMwpAUC72h) and between Baseline and the morning of Day 6 (POMwpAUC120h)

Area under the curve (AUC) will be calculated as the area under the curve from zero to 72 and 120 hours, using the trapezoidal rule divided by the observation time.

$$POM_{WP}AUC_{72} = \frac{1}{t_3}\sum_{i=1}^{3}\frac{1}{2}(POM_{WP}(t_{i-1}) + POM_{WP}(t_i)) \times (t_i - t_{i-1})$$
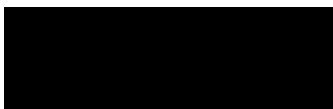
$$POM_{WP}AUC_{120} = \frac{1}{t_4}\sum_{i=1}^{4}\frac{1}{2}(POM_{WP}(t_{i-1}) + POM_{WP}(t_i)) * (t_i - t_{i-1})$$

The dates and time of trial medication intake related to the POMwp assessments will be the basis for the calculation of respective time intervals:

$t_0 = 0$ is related to POM assessment 1 (Day 1 pre-dose),

$$t_i = \left(\left[actual\ date_{intake\ related\ to\ POMWP\ assessment_{i+1}} - actual\ date_{first\ intake\ (visit\ 1)}\right] \times 24\right)$$
$$+ \left(actual\ time_{intake\ related\ to\ POMWP\ assessment_{i+1}} - actual\ time_{first\ intake\ (visit\ 1)}\right)$$

t_1, t_2, t_3, t_4 are related to POM assessments 2 (Day 1,120 min), 3 (Day 2, 120 min), 4 (Day4, 120min) and 5 (Day 6, 120min), respectively.

The ANCOVA model will include treatment, country, and wp-site (back/neck) as fixed effects and the baseline POMwp 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 following SAS code will be used to fit the ANCOVA model:

```
proc mixed data=<data> method=reml;

class treatment country wp_site;

model AUC = treatment country wp_site baselinePOMwp / solution;

lsmeans treatment / pdiff cl;

run;
```

where

AUC = POMwpAUC72h

Treatment = Treatment group (Ibuprofen + caffeine/ibuprofen/placebo).

Country = Germany/Russia.

Wp_site = Worst procedure site (back/neck).

BasePOMwp = Baseline POMwp.

14.2.2. MISSING DATA

For the calculation of POMwpAUC72h and POMwpAUC120h, the following imputation rules for missing POMwp 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 POMwp value.

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Linear interpolation formula:

$$y - y_1 = \frac{y_2 - y_1}{x_2 - x_1}(x - x1)$$

Where the two known points are given by the coordinates (x1,y1) and (x2,y2), the linear interpolant is the straight line between these points. The planned assessment time are presented in in Table 6: Planned Assessment Times below.

Table 6: Planned Assessment Times

Assessment	t_i
1 (Baseline)	$t_0 = 0$
2 (Day 1, 120min)	$t_1 = 2h$
3 (Day 2, 120min)	$t_2 = 26h$
4 (Day 4, 120min)	$t_3 = 74h$
5 (Day 6, 120min)	$t_4 = 122h$

14.2.3. ANALYSIS OF OTHER SECONDARY EFFICACY VARIABLES

14.2.3.1. Change in Pressure Algometry (PA) between baseline and Day 2 morning, 2 hours after drug intake

Analysis will be analogously to the primary endpoint using all available longitudinal PA observations. All available time points, baseline, Day 1 (120 min), Day 2 (120 min) will be used.

The model will be applied to the analysis of change from baseline (Day 1 [pre-dose]) in PA at Day 1 (120 min) and Day 2 (120 min).

The same PROC MIXED model will be applied as detailed for the primary analysis (refer to section 14.1.3: Mixed model repeated measures (MMRM)), POMwp will be replaced by PA.

14.2.3.2. Global assessment of efficacy by the patient at the end of treatment (Day 6 morning)

The number and percentage of patients within each category will be presented by treatment group.

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 will be used. The likelihood-ratio test will be used to test for treatment differences. Adjusted odds ratios together with 95% profile likelihood based confidence intervals and the associated p-values will be used to quantify the treatment effect, comparing ibuprofen + caffeine to ibuprofen and to placebo only.

An ordinal logistic regression model will be fitted. The covariates of interest in terms of efficacy are treatment, country and wp-site (back/neck) and will be included in the model as such:

proc genmod data=<data> order=descending;

class treatment country wp_site;

model effic = treatment country wp_site /

dist=multinomial aggregate=treatment link=cumlogit;

lsmeans treatment / diff cl;

run;

where:

Effic   = Efficacy rating reported by the patient at the end of treatment (Day 6 morning)

(coded as 0 = poor, 1 = fair, 2 = good, 3 = very good).

Treatment   = Treatment group (Ibuprofen + caffeine/ibuprofen/placebo).

Country   = Germany/Russia.

Wp_site   = Worst procedure site (back/neck).

14.2.3.3. Missing Data

For the calculations of global assessment of efficacy by the patient at the end of treatment, the following imputation rules for missing efficacy assessments will be applied:

- Missing entries for the assessment of efficacy will be assigned the least favourable category (0 = poor), if a patients has discontinued the study due to lack of efficacy as recorded on the Termination of Trial Medication eCRF.

- Missing assessment resulting from early discontinuation that is clearly not related to treatment of the patient will not be imputed.

14.2.3.4. Number of patients with a decrease in POMwp of at least 30% between Baseline and Day 2 morning, 2 hours after drug intake

This endpoint will be analysed using 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% Wald confidence intervals will be used to quantify the effect of treatment, comparing all treatments to the treatment of ibuprofen + caffeine as the reference treatment. In addition, residual plots and goodness of fit measures will be evaluated, but not displayed in output.

A logistic regression model for the binary, dependent variable will be fitted. The covariates of interest are treatment (Ibuprofen + caffeine/ibuprofen/ placebo) and country (Germany/Russia) and wp-site (back/neck) and will be included in the model as such:

proc genmod data=<data> order=descending;

class treatment country wp_site;

model POMwp_30 = treatment country wp_site / dist=bin;

run;

where:

POMwp_30   = Yes (=1), if % reduction in POMwp from baseline ≥30%, no (=0) otherwise.

Treatment   = Treatment groups (Ibuprofen + caffeine/ibuprofen/placebo).

Country   = Germany/Russia.

Wp_site   = Worst procedure site (back/neck).

14.2.3.5.   Number of patients with a decrease in POMwp of at least 50% between Baseline and Day 2 morning, 2 hours after drug intake

This endpoint will be analysed analogously to 14.2.3.4: Number of patients with a decrease in POMwp of at least 30% between Baseline and Day 2 morning, 2 hours after drug intake.

The POMwp_30 will be replaced by POMwp_50 = yes (=1), if % reduction in POMwp from baseline ≥50%, no (=0) otherwise.

14.2.3.6.   Time to first meaningful POMwp relief (≥2) within 2 hours after the first dose of trial medication

For this endpoint a Kaplan-Meier analysis will be performed and stratified log-rank test adjusting for the categorical variables country and wp-site will be used to test the difference between treatment groups.

Kaplan-Meier estimates for median time to first meaningful POMwp relief score of ≥2 with 95% CI for the median, 25th and 75th percentiles, adjusted for country and wp-site as covariates in the model will be displayed. Kaplan-Meier estimates for time to first meaningful POMwp relief score of ≥2 will be displayed graphically by treatment group using Kaplan-Meier (KM) curves.

Patients who experienced a meaningful POMwp relief score of ≥2 will be counted as patients with events, while patients with no event will be censored at 2 hours after first use of trial medication. The survival distribution of time to first meaningful POMwp relief score of ≥2 will be compared between treatment groups by means of the log-rank test. The SAS® procedure PROC LIFETEST including covariates, country and wp-site, will be used as follows:

```
proc lifetest data=<data> outsurv=grapdata plots=(s) gout=graphname;
        time time*censor(1);
        strata wp_site country / group=treatment;
run;
```

where

Time   = Time (hours) to first POMwp relief score of ≥2.

Censor(1)   = Indicates patients with no event of meaningful POMwp relief score of ≥2 (1=censored).

Wp_site   = Worst procedure site (back/neck).

Country   = Germany/Russia.

Treatment   = Treatment groups (Ibuprofen + caffeine/ibuprofen/placebo).
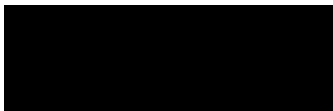
Time point of first meaningful POMwp relief score:

• Chronologically sorting all dates and times of the POMwp relief score within a patient and selecting the earliest date/time of the POMwp relief score ≥2 available.

Patients with an event:

• The time point at which the first meaningful POMwp review is observed is used to identify the time interval in which the relief was noted.

Patients with no event (censored):

• The time point at which the first meaningful POMwp review is observed > 120 min.

The following time intervals will be displayed:

• 0 - ≤10 min,

• >10 - ≤20 min,

• >20 - ≤30 min,

• >30 - ≤60 min,

• >60 - ≤120 min

• > 120 min

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Author:

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Version Date: 29AUG2017

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Effective Date: 01Apr2016

15.   SAFETY OUTCOMES

The Treated set will be used all safety analyses. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

15.1.   ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

15.1.1.   ALL ADVERSE EVENTS

The number of patients with at least one AE in each category (patients with multiple AEs in each category will be counted only once in each category) will be presented.

The percentage (%) of patients with at least one AE in each category will be calculated relative to the total number of patients in the Treated set by treatment group.

The incidence tables will be presented by primary SOC by total descending frequency and by PT by total descending frequency within SOC. Where different SOCs or PTs have the same total frequency, the SOCs or PTs will be sorted alphabetically.

All AEs and SAEs will be coded using the most recent MedDRA version. Uncoded terms will be displayed last within the category Uncoded and utilising the verbatim term entered on the eCRF as PT (for example Uncoded/Soft tummy).

Intensity:

- If a patient reports an AE more than once within that SOC/ PT, the AE with the worst case intensity will be used in the corresponding by worst intensity summaries.

- Patients with multiple events in each category are counted only once in each category at worst intensity (increasing intensity: mild, moderate and severe).
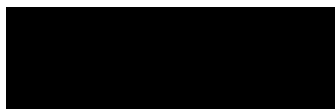
Relationship to trial medication:

- Causal relationship between the event and the trial medication:

  o Yes: Related.
  o No: Not related.

Serious adverse events (Including Death):

- Serious AEs are those events where was event serious is indicated as yes. The AEs leading to death are those events where outcome of event is recorded as fatal and/or criteria for SAE is recorded as results in death.

Adverse events leading to discontinuation of trial medication:

- Adverse events leading to discontinuation of the trial medication are those events where action taken is indicated as drug permanently discontinued.

Adverse events of special interest:

- Adverse events of special interest are those events where adverse event of special interest is indicated as yes on the eCRF.

  o Refer to the section 5.3.7.1 of the clinical trial protocol for the definition of AESIs (hepatic injury).

15.1.2. OTHER SIGNIFICANT ADVERSE EVENTS (ACCORDING TO ICH E3)

Other significant adverse events (according to ICH E3) include the following events:

- Marked laboratory abnormalities (other than those meeting the definition of serious).

  o These will be identified through a medical review of all the reported adverse events.

- Any event that led to an intervention, including withdrawal of trial medication, dose reduction, or significant additional concomitant therapy (other than those reported as serious adverse events).

  o The events leading to trial medication withdrawal or dose reduction will be identified as any event where the action taken is indicated as:
    - Dose permanently reduced.
    - Drug permanently discontinued.
  o The events leading to significant additional therapy will be identified through a medical review of all the reported adverse events.

15.2. DERIVATIONS

Adverse events are classified according to the event start date as note in Table 4: Study Periods.

Refer APPENDIX 1: Partial Date Conventions for handling of partial dates for AEs.

In the listing, adverse events of special interest will be indicated by means of *, other significant adverse events (according to ICH E3) will be indicated by means of a #.

|	
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Author:	Version Number: 1.0
	Version Date: 29AUG2017

Template No: CS_TP_BS016 Revision 4   Reference: CS_WI_BS005
Effective Date: 01Apr2016

17. REFERENCES

BI1335.5 Clinical Trial Protocol, Version 2.0 Final, dated 05AUG2016.

BI1335.5 Annotated Study Book, Version 3.0, 16DEC2016.

## APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings, these dates will only be used for the assignment of records to the relevant study periods.

ALGORITHM FOR TREATMENT- EMERGENCE OF ADVERSE EVENTS:

Adverse event dates (start and end) are required items in the eCRF, therefore cannot be missing or partial.

If adverse event time is missing, then first dose date (without the time) will be used to classify the adverse event as treatment-emergent or not.

IMPUTATION ALGORITHM FOR PARTIAL DATE FOR HISTORICAL AND CONCOMITANT THERAPIES:

- Start date:
    - If the day of the start date is missing, then start date is set to first day of the month.
    - If the day and month of the start date are missing, then the start date is set to 1st January of the year.

- End date:
    - If the day of the end date is missing, then the end date is set to last day of the month.
    - If the day and month of the end date are missing, then the end date is set to 31st December of the year.

Document Approval Signature(s)

This document has been signed electronically in compliance with ███████ electronic signature policies and procedures. This page is a manifestation of the electronic signatures, which may be confirmed within the ███████ source system in accordance with ████████ records retention policies.

Note: the Title field in the signature block has been intentionally left blank.

UserName: ████████████████████
Title:
Date: Wednesday, 06 September 2017, 08:12 AM   Eastern Time
Meaning: I Approve the Document
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