Trial Protocol

Title of The Clinical Trial

|  |  |
| --- | --- |
| SponsorCompany with addressorUniversity of CologneAlbertus-Magnus-Platz50923 KölnGermany | Principal Coordinating Investigator:NameHospitalCologne University HospitalKerpener Strasse 6250937 CologneGermany |

Trial protocol code: xxx

ISRCTN: xxx

or registration in another trial register approved by the World Health Organisation (WHO)

EudraCT number: xxx

Version of 29.03.2018, Version V08

The information in this trial protocol is strictly confidential. It is for the use of the sponsor, principal investigator, trial personnel, ethics committee, the authorities, and trial subjects only. This trial protocol may not be passed on to third parties without the express agreement of the sponsor or the Principal Coordinating Investigator (PCI, “Leiter der klinischen Prüfung (LKP)”).

Authors G Grass; University of Cologne (Sponsor); CTC Cologne

This document is subject to the UVM licence for unprotected content (<http://www.ifross.de/Lizenzen/LizenzFuerFreieInhalte.html>) and may only be used if the license is adhered to. This document must always be passed on with a copy of the licence. If you use this document as the basis for a trial protocol or when planning a clinical trial, please mention this in the trial protocol as appropriate, or include it in the reference list.

Contact address of author: guido.grass@uni-koeln.de, uni-sponsor@uk-koeln.de, info@zks-koeln.de

Particular thanks for valuable input are due to Dr. Claudia Weiß, Prof. Dr. Martin Hellmich

Advice on the use of this document

This template is intended to facilitate the preparation of trial protocols, both commercial and non-commercial. The texts of the section headings take into account the ICH E3 and E6 Guidelines.

The heading texts and numbering must not be changed. Generally, no first-, second- or third-level headings may be added or deleted, although the following adjustments are permitted:

Since the template is based on regulatory requirements primarily concerned with the clinical testing of pharmaceuticals, terms such as investigational medicinal product and study medication must be adjusted when using the template to prepare study protocols for the testing of medical products or devices. This applies, for example, to the headings in Sections 7.2 to 7.4. Because of the many possible but very different requirements in these sections, no suggested texts have been prepared. Requirements are also subject to regular revision and these should also be taken account of when preparing texts for these sections.

This template is based on regulatory requirements in Germany for trials with medicinal products. When preparing texts for multinational trials, attention should therefore be paid to requirements in other countries.

If this template is adapted for trials with medical devices please be aware that processes and terminology differ in trials with medical devices and medicinal products significantly.

Explanations are given in green text in italics. In some sections, blue sample texts or reminders are given. In both cases, the appropriateness of the given statements should be checked for the clinical trial in question. This applies in particular to the sample texts, which should not be simply copied without critical review. The sample texts and many of the reminders have been formulated for the conduct of a multicentre study for which the University of Cologne is the sponsor of an investigator-initiated trial (IIT). In such a case, many of the tasks will be performed by the PCI / LKP and the Clinical Trials Centre Cologne (CTCC) in Cologne. If tasks are to be performed by other persons or bodies, the texts should be adjusted accordingly.

**Before using this template, please delete this and the previous text.**

**The authors can accept no responsibility for the accuracy of any of the suggestions made in this document. All users should check the accuracy against the valid regulations and guidelines. We would be grateful for any information on errors or comments:** **guido.grass@uni-koeln.de****;** **uni-sponsor@uk-koeln.de****.**

# Signatures

All persons who made a significant contribution to the preparation of the trial protocol should sign this page.

Name (PCI, Principal Coordinating Investigator)

On behalf of the sponsor Signature Date
University of Cologne

Name

Medical contact of the sponsor Signature Date
Hospital and Ambulatory Clinic for xxx,

Cologne University Hospital

If the medical contact of the sponsor and the PCI / LKP is the same person, this second signature can be omitted and the words ‘Medical contact of the sponsor’ should be added to the above.

Name
Statistician Signature Date
Institute of Medical Statistics and Computational Biology (IMSB)

University of Cologne

# Synopsis

|  |  |
| --- | --- |
| Sponsor: | Company with address / contact data orUniversity of CologneRepresented by:Name (Principal Coordinating Investigator, PCI)Department for xxx Hospital and Ambulatory Clinic Cologne University HospitalKerpener Strasse 6250937 CologneGermany |
| Principal Coordinating Investigator: | See aboveIt may be necessary to add national representatives of the sponsor here, especially in the case of multinational, multicentre trials. |
| Title of the clinical trial: |  |
| Indication: |  |
| Phase: | Phase xxx (I to IV) clinical trial |
| Type of trial, trial design, methodology: | Single or multicentre, multinational clinical trialTwo, three or four arms, randomised, single-blind or double-blind, placebo-controlled, parallel-group or crossover design |
| Number of subjects: | XXX per treatment group (total xxx) |
| Primary trial objective: |  |
| Study end points: | Primary end point:* xxx

Secondary end point:* xxx

Other variables:* xxx
 |
| Diagnosis and Principal inclusion and exclusion criteria: | Medical condition or disease to be investigated:* xxx

Principal inclusion criteria:* xxx

Principal exclusion criteria:* xxx
 |
| Name of investigational medicinal product (IMP): |  |
| Investigational medicinal product – dosage and method of administration: |  |
| IMP or therapy used as a comparator – dosage and method of administration: |  |
| Duration of treatment: | Description of the duration of treatment (may be different for investigational medicinal product [IMP] and comparator) and any follow-up period, i.e. overall duration of the trial in each trial subject and how this time is distributed across different trial phases |
| Time plan: |

|  |  |
| --- | --- |
| First patient first visit (FPFV): | Q III 2018 |
| Last patient first visit (LPFV): | Q III 2020 |
| Last patient last visit (LPLV): | Q IV 2020 |
| End of trial: | Q IV 2020 |
| Final study report: | Q IV 2021 |
| *(See Chap. 4.1.1)* |  |

 |
| Statistician: | NameInstitute of Medical Statistics und Computational Biology (IMSB)University of CologneKerpener Str. 6250937 CologneGermany |
| Statistical methods: | Randomisation: blocks of variable size stratified according to trial site and xxx. A centralized randomisation will be performed. Interim analysis - adaptation of the trial design according to O’Brien-Fleming limits if necessary, and evaluation using the inverse-normal method.Evaluation of primary target variables: analysis of variance (factors: treatment and trial site; type II sums of squares) |
| GCP compliance: | The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.If appropriate, mention other regulatory documents here (e.g. AMG, X-Ray Regulations [Röntgenverordnung; RöV] or the Radiation Protection Regulations [Strahlenschutzverordnung; StrlSchV], medical devices act [MPG]).  |
| Financing: | List all sources of financing. |

# Table of contents

[I. Signatures 3](#_Toc510077461)

[II. Synopsis 4](#_Toc510077462)

[III. Table of contents 7](#_Toc510077463)

[III.a) List of tables 12](#_Toc510077464)

[III.b) List of figures 12](#_Toc510077465)

[IV. Abbreviations 13](#_Toc510077466)

[1. Introduction 14](#_Toc510077467)

[2. Objectives of the clinical trial 15](#_Toc510077468)

[2.1. Rationale for the clinical trial 15](#_Toc510077469)

[2.2. Primary objective 15](#_Toc510077470)

[2.3. Secondary and other objectives 15](#_Toc510077471)

[3. Organisational and administrative aspects of the trial 16](#_Toc510077472)

[3.1. Sponsor 16](#_Toc510077473)

[3.2. Principal Coordinating Investigator 16](#_Toc510077474)

[3.3. Statistics 16](#_Toc510077475)

[3.4. Data Monitoring Committee 17](#_Toc510077476)

[3.5. Further committees 17](#_Toc510077477)

[3.5.1. Steering Committee 18](#_Toc510077478)

[3.5.2. Advisory Committee 18](#_Toc510077479)

[3.5.3. Review Board 18](#_Toc510077480)

[3.6. Study laboratories and other technical services 18](#_Toc510077481)

[3.7. Central organisation units 18](#_Toc510077482)

[3.8. Principal investigators and trial sites 19](#_Toc510077483)

[3.8.1. Requirements for principal investigators and trial sites 19](#_Toc510077484)

[3.9. Financing 19](#_Toc510077485)

[4. Trial conduct 21](#_Toc510077486)

[4.1. General aspects of trial design 21](#_Toc510077487)

[4.1.1. Time plan 21](#_Toc510077488)

[4.2. Discussion of trial design 22](#_Toc510077489)

[4.3. Risk Benefit Assessment 22](#_Toc510077490)

[4.3.1. Known Potential Risks 22](#_Toc510077491)

[4.3.2. Known Potential Benefits 23](#_Toc510077492)

[4.3.3. Assessment of Potential Risks and Benefits 23](#_Toc510077493)

[4.4. Selection of trial population 23](#_Toc510077494)

[4.4.1. Inclusion criteria 24](#_Toc510077495)

[4.4.2. Exclusion criteria 24](#_Toc510077496)

[4.5. Withdrawal of trial subjects after trial start 25](#_Toc510077497)

[4.5.1. Procedures for premature withdrawal from treatment during the trial 26](#_Toc510077498)

[4.6. Closure of trial sites/Premature termination of the clinical trial 26](#_Toc510077499)

[4.6.1. Closure of trial sites 26](#_Toc510077500)

[4.6.2. Premature termination of trial 26](#_Toc510077501)

[4.7. Treatment 27](#_Toc510077502)

[4.7.1. Treatments to be given 27](#_Toc510077503)

[4.7.2. Description of investigational medicinal product 27](#_Toc510077504)

[4.7.2.1. Manufacture of the investigational medicinal product 28](#_Toc510077505)

[4.7.2.2. Labelling of investigational medicinal product 28](#_Toc510077506)

[4.7.2.3. Storage of investigational medicinal product 28](#_Toc510077507)

[4.7.3. Compliance with treatment / Dispensing and return of investigational medicinal product 28](#_Toc510077508)

[4.7.4. Assignment of trial subjects to treatment groups 28](#_Toc510077509)

[4.7.5. Selection of dosage of investigational medicinal product 29](#_Toc510077510)

[4.7.6. Time of administration and adjustments to dosage of the investigational medicinal product in the individual trial subject 29](#_Toc510077511)

[4.7.7. Blinding 29](#_Toc510077512)

[4.7.7.1. Unblinding 29](#_Toc510077513)

[4.7.8. Previous and concomitant medication 30](#_Toc510077514)

[4.7.8.1. Rescue therapy for emergencies 30](#_Toc510077515)

[4.7.9. Continuation of treatment after the end of the clinical trial 30](#_Toc510077516)

[4.8. Efficacy and safety variables 30](#_Toc510077517)

[4.8.1. Measurement of efficacy and safety variables 30](#_Toc510077518)

[4.8.1.1. Primary target variable 30](#_Toc510077519)

[4.8.1.2. Secondary and other target variables 30](#_Toc510077520)

[4.8.1.3. Safety analysis 30](#_Toc510077521)

[4.8.1.4. Description of visits 31](#_Toc510077522)

[4.8.2. Rationale for assessment procedures 31](#_Toc510077523)

[4.8.3. Pharmacokinetics/Determination of drug levels 31](#_Toc510077524)

[4.9. Data quality assurance 31](#_Toc510077525)

[4.9.1. Monitoring 31](#_Toc510077526)

[4.9.2. Audits/Inspections 33](#_Toc510077527)

[4.10. Documentation 33](#_Toc510077528)

[4.10.1. Data management 33](#_Toc510077529)

[4.10.2. Archiving 34](#_Toc510077530)

[5. Ethical and regulatory aspects 35](#_Toc510077531)

[5.1. Ethics committee 35](#_Toc510077532)

[5.2. Ethical considerations 35](#_Toc510077533)

[5.3. Legislation and guidelines 35](#_Toc510077534)

[5.4. Notification of the authorities, approval and registration 35](#_Toc510077535)

[5.5. Obtaining informed consent from trial subjects 36](#_Toc510077536)

[5.6. Insurance of trial subjects 36](#_Toc510077537)

[5.7. Data protection 37](#_Toc510077538)

[6. Statistical methods and sample size calculation 38](#_Toc510077539)

[6.1. Statistical and analytical plan 38](#_Toc510077540)

[6.1.1. Analysis population 38](#_Toc510077541)

[6.1.2. Description of trial subject groups 39](#_Toc510077542)

[6.1.3. Primary target variable 39](#_Toc510077543)

[6.1.4. Secondary target variables 39](#_Toc510077544)

[6.1.5. Subgroup analyses 39](#_Toc510077545)

[6.1.6. Interim analysis 39](#_Toc510077546)

[6.2. Sample size calculation 39](#_Toc510077547)

[7. Safety 41](#_Toc510077548)

[7.1. Definitions of adverse events and adverse drug reactions 41](#_Toc510077549)

[7.1.1. Adverse event 41](#_Toc510077550)

[7.1.2. Adverse drug reaction 41](#_Toc510077551)

[7.1.3. Serious adverse events and serious adverse reactions 41](#_Toc510077552)

[7.1.4. Unexpected adverse drug reaction 42](#_Toc510077553)

[7.1.5. Suspected unexpected serious adverse reactions 42](#_Toc510077554)

[7.1.6. Adverse events of special interest 42](#_Toc510077555)

[7.2. Documentation and follow-up of adverse events 43](#_Toc510077556)

[7.2.1. Documentation of adverse events and adverse drug reactions 43](#_Toc510077557)

[*7.2.1.1.* *Exceptions from AE documentation* 44](#_Toc510077558)

[7.2.2. Severity of the adverse event 44](#_Toc510077559)

[7.2.3. Causal relationship between adverse event and investigational medicinal product 44](#_Toc510077560)

[7.3. Reporting of serious adverse events, adverse events of special interest, pregnancy and changes in risk-benefit assessment 46](#_Toc510077561)

[7.3.1. Reports from the investigator to the sponsor 46](#_Toc510077562)

[7.3.2. Assessment of SAEs by the sponsor 47](#_Toc510077563)

[7.3.3. Unblinding for SUSAR when treatment is blinded 47](#_Toc510077564)

[7.3.4. Notification of ethics committee and competent authority 48](#_Toc510077565)

[7.3.5. Review and reporting of changes in the risk-benefit ratio 48](#_Toc510077566)

[7.3.6. Informing the Data Monitoring Committee 49](#_Toc510077567)

[7.3.7. Informing the investigators 49](#_Toc510077568)

[7.3.8. Informing the marketing authorisation holder 49](#_Toc510077569)

[7.4. Annual safety report (DSUR) 49](#_Toc510077570)

[8. Trial results and publication 51](#_Toc510077571)

[8.1. Reports 51](#_Toc510077572)

[8.1.1. Interim reports 51](#_Toc510077573)

[8.1.2. Final report 51](#_Toc510077574)

[8.2. Publication 51](#_Toc510077575)

[9. Amendments to the trial protocol 53](#_Toc510077576)

[10. References 54](#_Toc510077577)

[11. Appendices 55](#_Toc510077578)

[11.1. Trial sites with principal investigator and deputy 55](#_Toc510077579)

[11.2. Protocol Agreement Form 55](#_Toc510077580)

[11.3. Steering Committee 55](#_Toc510077581)

[11.4. Data Monitoring Committee 55](#_Toc510077582)

[11.5. Advisory Committee 55](#_Toc510077583)

[11.6. Study laboratories and other technical resources 55](#_Toc510077584)

[11.7. Sample labels for investigational medicinalris product (IMP) 55](#_Toc510077585)

[11.8. Patient informed consent form 55](#_Toc510077586)

[11.9. Prescribing information 55](#_Toc510077587)

[11.10. Confirmation of insurance 55](#_Toc510077588)

[11.11. Conditions of insurance 55](#_Toc510077589)

## List of tables

[Table 1: Time plan of the trial 22](#_Toc504990348)

[Table 2: Dosage of investigational medicinal product 31](#_Toc504990349)

[Table 3: Investigations during the clinical trial 34](#_Toc504990350)

## List of figures

[Figure 1: Trial flowchart 23](#_Toc504990351)

# Abbreviations

|  |  |
| --- | --- |
| **abbreviation** | **meaning** |
| AE | Adverse Event |
| BfArM | Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte) |
| CA | Competent authority (BfArM, PEI) |
| CRF | Case Report Form |
| DMC  | Data Monitoring Committee  |
| DSUR | Development Safety Update Report |
| EC | Ethics Committee |
| ISF | Investigator Site File |
| IMP | Investigational Medicinal Product |
| PCI | Principal Coordinating Investigator (Leiter der klinischen Prüfung, LKP) |
| PI | Principal Investigator |
| PEI | Paul-Ehrlich-Institut |
| SAE | Serious Adverse Event |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |

# Introduction

The introduction should be as short and concise as possible. Describe the background of the clinical trial in relation to the indication in the context of any findings from trials already known. Special mention should be made of previous trials, relevant results from clinical, preclinical and other testing or trials, and of trials with similar interventional methodology. This should be supported by references to relevant publications and, if appropriate, other important background information for the trial. A current systematic review should be considered as a basis for planning the trial. The introduction should include only information relevant to the trial, supporting the rationale for the trial and its objectives.

# Objectives of the clinical trial

## Rationale for the clinical trial

Provide a brief summary of the reasons for conducting the trial.

For detailed assessment of potential risks and benefits see section [4.3](#_Risk_Benefit_Assessment).

## Primary objective

Describe the primary objective of the trial in **clinical** terms / from clinical view (clinical relevance, expected patient benefit etc.) and in terms of the primary target variable. The suitability of the selected variables to fulfil the clinical objective and their measurement as well as methods of measurement are described in section 4.8, and their statistical evaluation in sections 6.1.3 und 6.1.4.

## Secondary and other objectives

Clinical description of secondary objectives

# Organisational and administrative aspects of the trial

In IITs the PCI may assume sponsor responsibilities. Therefore, responsibilities attributed to the sponsor will often be delegated to the PCI or other persons, institution and/or service providers.

In the following text responsibilities attributed to the sponsor may in some extend be delegated to the PCI or other persons, institution and/or service providers. Details are fixed in a separate document or contract. In general, for readability reasons only the sponsor and not its delegate is named throughout the text.

## Sponsor

Sponsor: University of Cologne

Represented by: Name
Hospital and Ambulatory clinic xxx
University Hospital Cologne
Kerpener Strasse 62
50937 Cologne

 Germany

## Principal Coordinating Investigator

Principal Coordinating

Investigator (PCI): Name

 Hospital and Ambulatory clinic XXX
Cologne University Hospital
Kerpener Strasse 62
50937 Köln
Germany

## Statistics

Statistician: Name
Institute of Medical Statistics and Computational Biology (IMSB)
University of Cologne
Kerpener Strasse 62
50937 Cologne
Germany

## Data Monitoring Committee

Definition and description of the tasks and working methods of the Data Monitoring Committee (DMC): checking of trial progress, safety data, checking of efficacy variables, for example as part of a blinded interim analysis, advising the sponsor on the continuation, modification or termination of the clinical trial based on interim results or safety results (see also Guideline EMEA/CHMP/EWP/5872/03 Corr).

This paragraph should include the description of information and data pathways. In case the DMC is involved in the reporting procedure (unblinding) for adverse events, this has to be taken into account (detailed description in Section 7.3.6). Be aware that a DMC is independent and therefore can have its own charter which determines its working procedures. (see also EMA “Guidline on Data Monitoring Committees”, EMEA/CHMP/EWP/5872/03).

If appropriate, the reasons why a DMC is not considered necessary should be given here.

A Data Monitoring Committee made up of independent experts will be set up. It consists of two physicians and a statistician who are not involved in the conduct of the trial and independent from the sponsor (see Section 11.4). The task of the DMC is to monitor the safety of the trial subjects in the clinical trial by periodically assessing the safety and efficacy of the trial therapy, and to monitor the integrity and validity of the data collected and the conduct of the clinical trial.

Throughout this process of surveillance, the DMC provides the sponsor with recommendations with regard to continuing the trial (e.g. termination or modification) based on the data collected. The data necessary for the DMC to fulfill this function are provided by the sponsor as determined by the DMC. Amongst other datasets, these must include listings providing information on serious adverse events and further variables that the DMC considers necessary at least every 6 months and when formal interim analyses are conducted.

## Further committees

This chapter and its subchapters are optional.

### Steering Committee

A Steering Committee (SC) may be formed who, together with the PCI, continuously monitor the progress of the trial, and who take, for example, majority decisions on all or selected questions.

A list of the members of the Steering Committee is given in Appendix 11.3.

### Advisory Committee

An advisory committee is often formed and is involved in various aspects of the trial, especially the planning and evaluation. The inclusion of opinion leaders can reduce the risk of conducting a clinical trial that does not find acceptance after completion.

A list of the members of the Advisory Committee is given in Appendix 11.5.

### Review Board

Often a committee is involved who assess efficacy or other relevant variables (blind review if applicable), or decide whether trial subjects have been treated in accordance with the protocol. Any other bodies can be mentioned in this section. The members of the Review Board and other bodies should also be listed in an appendix.

## Study laboratories and other technical services

This section should be used to describe the tasks that will be performed by other service providers. The names and addresses of the providers should be given in Appendix 11.6.

## Central organisation units

This section should be used to describe which departments or service providers will be performing the various tasks required. These activities are generally governed by separate contracts (e.g. sponsor contracts) and accompanying descriptions of the terms or reference of the tasks delegated (e. g. delegation list, task allocation list), including complete contact data for each unit.

Generally changes in contact data do not require an amendment and approval of the ethics committee and the competent authority. Independently of the legal requirements, changes of important contact data should be notified to EC and CA.

Project management: xxx

Monitoring: xxx

Data management: xxx

SAE management: *xxx*

Scientific advice: Name
Clinical Trials Centre Cologne (CTCC, ZKS Köln)
Gleueler Strasse 269
50935 Cologne
Germany
Tel.: +49 221 478 XXXX
Fax: +49 221 478 XXXX
Email: XY@zks-koeln.de

## Principal investigators and trial sites

This clinical trial will be carried out as a single-centre/multicentre open trial at XXX trial sites in Germany. If necessary, further qualified trial sites may be recruited to the trial.

A list of the trial sites with names of the principal investigators is given in Appendix 11.1.

The listing of trial sites, principal investigators and subinvestigators and further trial staff, will be kept and continuously updated in a seperate list, independent from the trial protocol. The final version of this list will be attached to the final report of the clinical trial.

### Requirements for principal investigators and trial sites

Describe the requirements that the trial sites and the principal investigators have to fulfill (e.g. proof of knowledge of regulatory procedures, experience with the conduct of the clinical testing of pharmaceutical preparations, special experience in the trial indication etc). The documents for the qualification of the clinical trial team are filed in the sponsor’s Trial Master File (TMF) as well as at the local trial site’s Investigator Site File (ISF).

## Financing

The clinical trial will be financed by a grant from the German Research Society (Deutsche Forschungsgesellschaft; DFG) / Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung; BMBF) (with grant number).

The clinical trial is financially supported by the pharmaceutical company [X]. Additionally the IMP is provided free of charge by [company].

A detailed financial plan does not form part of the trial protocol because it is archived separately and may be needed to gain approvals or to accompany contracts, or may be needed for submission to the ethics committee. However, all sources of financing must be listed here.

# Trial conduct

## General aspects of trial design

Please note the phase, aspects of trial methodology (e.g. double-blind, placebo-controlled, parallel-group/crossover / superiority / non-inferiority etc.), and a brief description of procedures to avoid or minimise bias (randomisation, blinding) here. One or two sentences should suffice.

### Time plan

Brief, concise description of the timing of the entire trial: brief description of the sequence and duration of the interventions, if necessary of the individual trial phases, and of any follow-up period, visit schedule (planned times and acceptable time windows), and a description of laboratory investigations and other diagnostic methods are appropriate. The use of tables and graphs is recommended.

Table 1: Time plan of the trial

|  |  |
| --- | --- |
| First patient first visit (FPFV): | Q III 2018 |
| Last patient first visit (LPFV): | Q III 2020 |
| Last patient last visit (LPLV): | Q IV 2020 |
| End of trial | Q IV 2020 |
| Final study report: | Q IV 2021 |

(see II. Synopsis)

End of the clinical trial

Define the end of the clinical trial, i.e. the date which determines when the period of notifications with the authorities terminates and which determines the deadline for the final study report to the authorities. In general the LPLV is taken as the end of the clinical trial, extended by the period within which AEs / SAEs are tracked (see section 7.2).

The end of trial is defined as 30 [days](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/days) after the [last](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/last) [patient](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/patient) last visit ([LPLV](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/LPLV)).

Figure 1: Trial flowchart



## Discussion of trial design

It is helpful for this discussion to incorporate the measures used to avoid bias (blinding, randomisation etc.) and why it is felt that these are necessary. The basis for the sample size (reference to statistical calculation of sample size) and the reasons for the type of comparison chosen (parallel-group, crossover) should be included. The choice of the comparator group should also be justified. If necessary, the use of a placebo group should be justified from an ethical point of view, and it should be stated whether or not any comparator treatment is the standard approach for the respective indication.

## Risk Benefit Assessment

This is an essential process of identifying potential risks associated with that trial, and assessing the likelihood of those risks occurring and resulting in harm. This risk assessment should include:

* the risks to participants safety in relation to the IMP and trial procedures,
* all other risks related to the design and methods of the trial (including risks to participants safety and rights, as well as reliability of results).

### Known Potential Risks

The following subsections should include a discussion of known risks and benefits to trial participants.

Include a discussion of known risks from both clinical and nonclinical studies. If the summary of product characteristics (SMPC) from a licensed or approved product is available, it may be used as the primary source of risk information. If the product is investigational, the IB should be the primary source of the risk information. In addition, relevant published literature may also provide relevant risk information.

Describe any medical, physical, psychological, social, legal, economic, or any other risks to participants, including both, short and long term risks.

If risks are related to trial procedures, it may be necessary to describe alternative procedures that have been considered and explain why alternative procedures are not included.

### Known Potential Benefits

Include a discussion of known potential benefits based on both clinical and nonclinical studies/data.

Note that payment to participants is not considered a “benefit.” Provision of “intensified care” is also not to be considered a benefit.

### Assessment of Potential Risks and Benefits

Include an assessment of potential risks and benefits, addressing each of the following:

* rationale for the necessity of exposing participants to risks and a summary of the measures to minimize the risks to participants,
* justification of the risks in relation to potential benefits.

## Selection of trial population

The characteristics of the trial population should be described in medical terms.

If necessary, the reasons for including, for example, children or subjects who are unable to give informed consent must be given and the measures taken to ensure the welfare of such groups must be described.

Reasons for gender distribution

The expected gender distribution must be given, as well as the reasons why this distribution in the population affected appears adequate to detect any gender-specific differences in efficacy or safety of the pharmaceutical preparation under testing. If appropriate, a cross reference to Section 6.1.5 should be added.

### Inclusion criteria

* *Trial indication*

A general rule is that inclusion and exclusion criteria should be described as unequivocally as possible. The inclusion criteria should also include the methods used to verify the indication (e.g. “findings demonstrated by coronary angiography that must be available in the trial subject’s records, not conducted earlier than 2 months before” or “at the discretion of the principal investigator/subinvestigator based on the trial subject’s medical history”). It must be kept in mind that inclusion and exclusion criteria may sometimes require trial-related (e.g. diagnostic) measures which have to be incorporated into the descriptions of the visits and cannot be performed until informed consent has been given.

* Age 18 years or above
* Written informed consent from the trial subject has been obtained

If healthy subjects are to be enrolled, the meaning of ‘healthy’ and how this is established must be defined.

### Exclusion criteria

* Participation in other interventional trials
* List contraindications according to theSummary of medicinal Product Characteristics, SmPC, the Fachinformation in Germany) or the Investigator’s Brochure, if appropriate.
* Use of drugs with significant interaction with the investigational product

If appropriate, list all relevant drugs and/or substances. If the categories of drugs/substances are named here a detailed list should be attached.

* Diseases or findings that may have a significant effect on the target variables and which may therefore mask or inhibit the therapeutic effect under investigation
* Pregnant women and nursing mothers
* Failure to use highly-effective contraceptive methods(this may also apply to the trial subject’s partner depending on the investigational product (IMP)). The following contraceptive methods with a Pearl Index lower than 1% are regarded as highly-effective:
	+ Oral hormonal contraception (‘pill’) (as far as its efficacy is not expected to be impaired during the trial, e.g. by IMPs that cause vomiting and diarrhoea, adequate safety cannot be assumed)
	+ Dermal hormonal contraception
	+ Vaginal hormonal contraception (NuvaRing®)
	+ Contraceptive plaster
	+ Long-acting injectable contraceptives
	+ Implants that release progesterone (Implanon®)
	+ Tubal ligation (female sterilisation)
	+ Intrauterine devices that release hormones (hormone spiral)
	+ Double barrier methods

This means that the following are not regarded as safe: condom plus spermicide, simple barrier methods (vaginal pessaries, condom, female condoms), copper spirals, the rhythm method, basal temperature method, and the withdrawal method (coitus interruptus).

The regulations for contraception are derived from Guideline ICH E8 Chapter 3.2.2.1 Selection of subjects together with ICH M3 Note 4

* Persons with any kind of dependency on the principal investigator or employed by the sponsor or principal investigator
* Legally incapictated persons
* Persons held in an institution by legal or official order

## Withdrawal of trial subjects after trial start

* Withdrawal from treatment
* Withdrawal from investigations
* Withdrawal from documentation

This section should describe, a) when and how trial subjects are to be withdrawn from the study / the treatment with the IMP, b) what findings at what time points are to be documented for trial subjects who are withdrawn, and c) whether and how trial subjects are to be replaced.

CAVE: The subsequent exclusion of clinical trial subjects should be avoided in order to permit a meaningful analysis according to the intention-to-treat principle. An exclusion from the therapy does not necessarily mean e. g., an exclusion of further investigations or further documentation.

### Procedures for premature withdrawal from treatment during the trial

Describe the appropriate data with reasons, further treatment, follow-up of the trial subject etc.

## Closure of trial sites/Premature termination of the clinical trial

### Closure of trial sites

Describe here criteria that would result in the sponsor considering closing the trial site and any escalation schedules / procedures planned (schedule for transfering information e.g. from monitor to project manager to PCI to Steering Committee).

### Premature termination of trial

The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination shall undergo a final examination which must be documented. The sponsor must be informed without delay if any principal investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

* The risk-benefit balance for the trial subject changes markedly
* It is no longer ethical to continue treatment with the IMP
* The sponsor considers that the trial must be discontinued for safety reasons (e.g. on the advice of the DMC)
* An interim analysis or results of other research show that one of the trial treatments is superior or inferior to another
* It is no longer practicable to complete the trial

The sponsor decides on whether to discontinue the trial in consultation with the PCI, DMC, SC, Advisory Board and trial statistician.

## Treatment

### Treatments to be given

Provide a detailed, comprehensible description of the treatments that will be given in each treatment group in the trial. The description must cover the entire duration of treatment, mode of administration, duration and dosage. It must be clearly stated how long the trial treatment will be continued and, if there is a follow-up observation period, how long this will be in each trial subject. If any of these treatment measures deviate from clinical standards in everyday practice or from guidelines, this must also be clearly stated.

### Description of investigational medicinal product

Description of the IMP: composition, concentration, supplier of placebo or comparator. Details of shelf-life, especially for trials with long treatment periods, should be noted. In addition, mention measures to be taken if the expiry date exceeds during the study. It should be noted that the placebo or comparator has to be declared as an investigational medicinal product.

Trade name:

INN (International Nonproprietary Name)/active substance:

ATC-Code:

Presentation:

Dose:

Manufacturer (or marketing authorisation holder if applicable):

Already approved for the following indication:

If the IMP has already been approved for use in humans, give a summary of the indication and contraindications, if appropriate.

#### Manufacture of the investigational medicinal product

If manufacturing processes are necessary (including e.g. packaging, outer packaging or labeling), a manufacturing authorisation for the Investigational medicinal product(s) is needed, which means that a corresponding supplier (manufacturer, contract manufacturer, [dispensary](http://dict.leo.org/ende?lp=ende&p=Ci4HO3kMAA&search=dispensary&trestr=0x8001) if applicable) needs to be involved.

#### Labelling of investigational medicinal product

Describe who is responsible for labelling. The planned text for the labels on the trial samples or accompanying text should be supplied in Appendix 11.7.

#### Storage of investigational medicinal product

If special storage conditions apply, these should be described here (e.g.cold chain, including safeguarding of compliance, etc.), including measures needed for verification (e.g. temperature logs).

### Compliance with treatment / Dispensing and return of investigational medicinal product

Strategies should be described to be used to improve treatment adherence and its monitoring.

Describe documentation and procedures for the dispensing and return of the IMP for the individual trial subject and the trial site, including what will happen to IMP returned or no longer needed. Describe persons responsible for drug accountability (IMP / comparator / placebo). Include a description of measures for managing the case of immediate product recall.

### Assignment of trial subjects to treatment groups

Describe the randomization or respective procedures and any stratification procedures, including a justification for the latter (e.g. detailed practical description of the randomization process; allocation rate/sequence; confidentiality terms; structure of the patient identification (PatID). The details given should not allow any predictability of the allocation sequence (for example, block length should not be given here).

### Selection of dosage of investigational medicinal product

Table 2: Dosage of investigational medicinal product

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Morning | Midday | Evening | At bedtime |
| Day 1 |  |  |  |  |
| Day 2 |  |  |  |  |
| Day 3 |  |  |  |  |

Give a justification of the dosage, schedule and duration of treatment.

### Time of administration and adjustments to dosage of the investigational medicinal product in the individual trial subject

Use this section to describe any dosage adjustments and when they are to be made in individual trial subjects. Also criteria for modification or termination of the allocated treatment should be mentioned (e.g. change in dosage due to adverse side effects, improvement or worsening of the disease or on patient's request). If necessary, reference must be made with regard to termination also to section 4.4.

### Blinding

Describe the blinding process (who will be blinded by which means – trial subject, principal investigator, rater, evaluator). If appliccable, describe why blinding or double-blinding is not sensible or not possible. If this is the case, describe measures taken to minimize bias (e.g. single-blinding of trial subject and blinding of evaluators). Include procedures to maintain blinding (access control for confidential documents like a randomisation list, description of practical / technical realisation references to manuals that describe the details of procedures.

#### Unblinding

Description of the emergency unblinding procedure to be conducted by the principal investigator (e.g. emergency envelopes and other unblinding measures), including measures to ensure that general blinding is maintained as far as possible. In general, the principal investigator should consult with the sponsor before unblinding, if possible. This section should also deal on the need to report cases of unblinding, including the associated process (information flow) of reporting (see also Section 7.3.3).

### Previous and concomitant medication

Describe permitted previous and concomitant therapies.

#### Rescue therapy for emergencies

*Describe rescue therapy.*

### Continuation of treatment after the end of the clinical trial

Describe how trial subjects should be treated after the end of the trial. It should be borne in mind that the IMP may need to be tapered off or may not allow to be discontinued without special measures.

## Efficacy and safety variables

This section should be used to describe how the clinical objectives will be achieved using measureable variables. The methods and times of measurement, documentation and evaluation should be described with reasons why the variables chosen are appropriate to achieve the objectives. Ensure consistency with the synopsis and statistical section.

[*According*](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/According)[*to*](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/to) *[Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj. 2013; 346:e7586] outcomes need to be defined “including the specific measurement variable (e.g. systolic blood pressure), analysis metric (e.g. change from baseline, final value, time to event), method of aggregation (e.g. median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.”*

### Measurement of efficacy and safety variables

#### Primary target variable

Describe the primary target variable and how it will be measured.

#### Secondary and other target variables

Describe secondary target variables and how they will be measured.

#### Safety analysis

*Describe targeted variables of the safety analysis and how they will be measured.*

#### Description of visits

Patient visits are carried out at the following timepoints (see table 3).

If necessary, insert further description of visits.

Table 3: Investigations during the clinical trial

| Visit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Trial day | Day 0 | Day 7 (+/- 3) | Day 14 (+/- 3) |  |  |  |  |  |  |
| Informed consent | x |  |  |  |  |  |  |  |  |
| Investigation 1 | x | x | x |  |  |  |  |  |  |
| Investigation 2 |  | x | x |  |  |  |  |  |  |

Duration of the clinical trial in the individual subject

The duration of the clinical trial for the individual patient should be given briefly.

### Rationale for assessment procedures

Discuss and justify the assessment procedures used for the efficacy and safety variables.

Recommendation: The specific guidelines (e.g. the Committee for Medicinal Products for Human Use (CHMP) and/or the core outcome sets of the COMET initiative (http://www.comet-initiative.org)) should be considered.

### Pharmacokinetics/Determination of drug levels

*Where pharmacokinetic studies or other analysis of drug levels have to be determined, this should be described here. Otherwise this chapter can be omitted.*

## Data quality assurance

### Monitoring

The trial sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject’s safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

If a risk adapted monitoring, e.g. according to/following ADAMON, is planned for the trial, this should be described and justified. Moreover, a short description of central quality assurance measures should be included.

The exact extent of the monitoring procedures is described in a separate monitoring manual. A brief summary should be given here including basic/minimum monitoring activities and central measures taken to ensure quality across trial sites as well as information pathways.

All principal investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in their activities at the trial site, as agreed in separate contracts with each trial site. The declaration of informed consent (see section 5.5) includes a statement allowing the monitor to compare the case report forms (CRFs) with the trial subject’s medical records (doctor’s notes, ECGs, laboratory printouts etc.). The principal investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

* To check the declarations of informed consent
* To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs)
* To check the completeness and accuracy of entries on the CRFs
* To validate the entries on the CRFs against those in the source documents (source data verification, SDV)
* To perform drug accountability checks
* To evaluate the progress of the trial
* To evaluate compliance with the trial protocol
* To assess whether the trial is being performed according to GCP at the trial site
* To discuss with the principal investigator aspects of trial conduct and any deficiencies found

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems.

[The](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/The) principal [investigator](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/examiner) [will](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/will) reasonablely [consider](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/consider) [the](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/the) corrective and preventive [measures](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/measures) [suggested](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/suggested) [by](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/by) [the](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/the) [monitor](http://de.pons.com/%C3%BCbersetzung/englisch-deutsch/monitor).

### Audits / Inspections

As part of quality assurance, the sponsor has the right to audit the trial sites and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject’s rights and trial subject safety are being maintained. The sponsor may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subjects’ medical records, drug accountability documentation, and trial-related correspondence).

The sponsor and all trial sites involved undertake to support auditors and inspections by the competent authorities at all times and to allow the persons charged with these duties access to the necessary original documentation.

All persons conducting audits will keep all trial subject data and other trial data confidential.

## Documentation

All data relevant to the trial are documented timely after measurement by the principal investigator / subinvestigator in the (electronic) case report form. The CRFs are signed by the principal investigator.

Describe rules for completion and correction (e.g. any corrections must leave the original entry legible and be initialled).

Define here, which data are regarded as source data and, if applicable, data that are to be recorded exclusively in the CRF. This means that under certain circumstances parts of the CRF will be considered as source data. This is usually restricted to forms filled out by the trial subjects themselves.

### Data management

The following text usually applies if data management activities are conducted by CTCC.

The IT infrastructure and data management staff will be supplied by the CTCC. The trial database will be developed and validated before data entry based on standard operating procedures at the CTCC. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked and the data exported for statistical analysis.

The arrival of CRFs at CTCC is documented and the CRFs checked for completeness. Independent data entry staff enters the data into a validated trial database using double data entry, and the data entered is compared. Plausibility checks are also conducted in the database. Discrepancies and implausible values are clarified in writing between the data manager and the trial site. The trial site has to answer these queries without unreasonable delay. Further details will be specified in the data management manual.

For remote data entry studies, the last paragraph above should read as follows:

The data will be entered online at the trial sites via the Internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The CTCC Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software. These electronic queries have to be answered by the trial site without unreasonable delay. Further details will be specified in the data management manual.

### Archiving

All essential trial documents according to ICH-GCP chapter 8 will be archived for at least 10 years unless longer times are foreseen by local regulatory requirements, this applies to both the investigator and sponsor part of the TMF.

More stringent archiving requirements apply to the clinical testing of pharmaceutical preparations that form part of a marketing authorisation application. Longer archiving periods may also apply to trials involving X-rays, radioactive substances or ionising radiation.

Detailed instructions for archiving are available on the homepage of the “Site Management System” at University hospital Cologne (https://clinicalsite.org/). We refer to “Documents / External archive” the clinic's internal SOP "archiving of paper-based study documents in an external archive (Fa. Hasenkamp)".

Digitization of paper based documentation must meet regulatory requirements, especially concerning quality assurance, completeness and correctness.

# Ethical and regulatory aspects

## Ethics committee

The clinical trial will not be started before favourable opinion of the competent ethics committee.

At each trial site the clinical trial will not be initiated unless favourable opinion has been given concerning the suitability of the trial site and the qualification of the principal investigator and his/her deputy.

## Ethical considerations

The present trial protocol and any amendments were and will be prepared in accordance with the principles of the Declaration of Helsinki.

If necessary, critical ethical aspects of the clinical trial should be discussed again here.

## Legislation and guidelines

The present clinical trial will be conducted in accordance with the principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation.

These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from trial subjects, adherence to the trial protocol, administrative documentation, documentation regarding the IMP, data collection, trial subjects’ medical records (source documents), documentation and reporting of adverse events (AEs), preparation for inspections and audits, and the archiving of trial documentation.

All principal investigators and other staff involved in the trial will be informed that local and national competent authorities as well as competent authorities from foreign countries and authorised representatives of the sponsor have the right to review trial documentation and the trial subjects’ medical records at any time.

## Notification of the authorities, approval and registration

Before the start of the clinical trial, all necessary documentation will be submitted to the competent authority for approval (Federal Institute for Drugs and Medical Products, Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]; Paul Ehrlich Institute, Paul-Ehrlich-Institut [PEI]). Local authorities will be notified according to applicable regulations.

Note: Other official bodies may also have to be notified, e.g. the Federal Office for Controlled Drugs (Bundesopiumstelle), the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz), or the State Environmental Offices (Landesumweltamt). Internal bodies have to be informed as applicable, e.g. DFS, Sponsor-QA, Studienkommission.

Before the trial is started, it will be registered under a register approved by the World Health Organisation (WHO) (http://www.who.int/ictrp/en/). Trials running at the University Hospital and the University of Cologne have to be registered at “Site Management System” (https://clinicalsite.org/), additionally.

## Obtaining informed consent from trial subjects

Trial subjects will be informed verbally and in writing in comprehensible language about the nature, scope and possible consequences by the trial principal investigator / subinvestigator. This includes consent to data access by representatives of the sponsor (e.g. monitors or auditors) and the competent authorities. The trial subject will be informed on potential benefits and possible risks including side effects of the IMP and placebo. Trial subjects will be informed that withdrawal of consent is possible at any time without giving reasons and without jeopardizing the subject’s further course of treatment. Subjects must not be enrolled into the trial unless they have consented to take part in writing.

The signed consent form is archived in the investigator site file at the trial site as original. Trial subjects receive copies of the written information sheet, and the signed informed consent form.

The informed consent form is supplied in Appendix 11.8.

The informed consent form and all other documents handed out to the trial subject and any recruitment advertisements will be submitted to the ethics committee for approval before use. Monitors will check that the most recent informed consent form was used before the trial subject’s inclusion and that it was dated and signed by the trial subject himself or herself.

## Insurance of trial subjects

All trial subjects enrolled are insured in accordance with regulatory requirements.

The University Hospital Cologne may provide insurance by its group insurance.

Travel accident insurance may also be required (if trial subjects have to show up for study specific investigations, for example).

## Data protection

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation.

Trial subjects will be informed that their pseudonymised data will be handled in accordance with applicable law. Subjects who do not agree to data handling as described in the informed consent form will not be enrolled into the trial.

# Statistical methods and sample size calculation

## Statistical and analytical plan

In this section, please bear in mind how missing data will be handled: usually, a total number of trial subjects is calculated that includes an estimated number of dropouts. It may be necessary or sensible to stipulate (and define) numbers of evaluable trial subjects (e.g. per protocol, valid for safety) and replace dropouts using a procedure described in the protocol.

Detailed information on planning, implementation and presentation of results of statistical analysis can be found in the ICH guidelines ICH E9 and E3. The used essential statistical procedures shall be specified by references.

### Analysis population

All analyses will be conducted on three trial populations:

The primary dataset for analysis is derived from the intention-to-treat (ITT; Full Analysis Set, FAS) population. This dataset includes all trial subjects enrolled into the trial and randomized.

The evaluation is carried out strictly in accordance with the allocation by randomization.

Any exceptions to this should be described here, e.g. trial subjects who never received any trial treatment even though they were randomized, or substantial deviations from any inclusion or exclusion criteria (see ICH E9).

The secondary dataset for analysis is derived from the per-protocol (PP) population. This dataset includes all trial subjects who were treated according to protocol and reached a defined endpoint in the trial.

The ITT analysis is standard for confirmatory trials seeking to demonstrate superiority of the IMP. The ITT and PP datasets are equally important in trials aiming to show non-inferiority.

The tertiary dataset for analysis is the safety population. This population includes all trial subjects who received any IMP or other trial treatment.

Describe how trial subjects will be assigned to these populations: which protocol deviations are seen and which will be regarded as major and which as minor. It is often sensible to put together a medical review group (e.g. PCI and one or two other experts) to review cases and reach a consensus on how they should be handled, using blinded data if possible (“blind review board”). The review should include those cases which can not be assigned to one of the populations by a logical algorithm to be performed before statistical analysis. Any aspects not clear at the time the protocol is prepared must be described in detail later in the statistical analysis plan, for example.

### Description of trial subject groups

How are the trial subject groups described?

### Primary target variable

Describe hypotheses and test procedures, and, if appropriate, list a reference to the statistical analysis plan.

### Secondary target variables

Please provide a detailed list and description of all secondary variables.

### Subgroup analyses

It is advisable to plan a subgroup analysis according to gender. A description should be provided concerning the differences to be possibly revealed given the expected distribution of the genders with the planned sample size.

### Interim analysis

Is a formal interim analysis planned? Describe the statistical methods (if necessary, refer to Section 6.2., especially if an adaptive design was chosen).

## Sample size calculation

Please specify the statistical rationale for the sample size. The text should include the assumptions and the statistical methods used to determine the sample size as well as details concerning the power of the trial. The sample size should also be justified in clinical terms (e.g. demonstration of a clinically relevant difference). In addition to the planned total number of trial subjects, the average number of subjects per trial site (with range) should be given. Strata, interim analyses and subgroup analyses should be included in the rationale as appropriate.

Also give the reasons why the gender distribution selected appears appropriate to demonstrate any gender-specific differences with regard to the efficacy or safety or the pharmaceutical preparation under testing in the population selected.

# Safety

## Definitions of adverse events and adverse drug reactions

### Adverse event

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment. *The adverse event may be, but is not restriced to: a new illness, worsening of a sign or symptom of the condition under treatment, the abnormal results of an examination (e.g., laboratory findings, electrocardiogram) or deterioration of a pre-existing medical condition, or a combination of two or more of these factors.*

*In general* ***all*** *AEs have to be documented. In general, AEs have to be documented beginning with first intake of the IMP. In some trials, it is sensible to document AEs from the time informed consent is given. This is the case for example in trials where trial-specific measures have to be taken* ***before*** *administration of the IMP. This section should therefore state from which point onwards AEs have to be documented and reported.*

Pregnancy

For reasons of drug safety, the occurrence of a pregnancy during the conduct of this trial is to be regarded as an AE. For details of special reporting requirements for pregnancy, see Section 7.2.2.

### Adverse drug reaction

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse drug reactions (ADR).

### Serious adverse events and serious adverse reactions

A serious AE (SAE) or serious ADR (SAR) is any untoward medical occurrence that at any dose

1. Results in death,
2. Is life-threatening at the time of the event,
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation,
4. Results in persistent or significant disability / incapacity,
5. Is a congenital anomaly or birth defect,
6. Is any other medical important event in the opinion of the investigator.

Inpatient hospitalisation is defined as any stay in hospital that includes at least one night (midnight to 06:00). Admission to hospital as an inpatient planned before the first admission of the IMP is not considered as SAE, but must be documented in a proper manner in the trial subject’s medical records and CRF (see Section 7.1.1).

### Unexpected adverse drug reaction

An unexpected ADR is an ADR, the nature or severity of which is not consistent with the applicable product information available for the IMP. ADRs listed in the *Investigator’s Brochure* are not regarded as unexpected.

*Also other documents might be suitable as reference, such as the Summary of Product Characteristics (SmPC, Information Sheet for Health Professionals [Fachinformation in Germany]) or other documents. For each IMP just one reference document (if applicable language version to be defined) has to be defined as reference.*

### Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

### Adverse events of special interest

An adverse event of special interest (AESI) is an adverse event that may not be serious but has special meaning or importance for the clinical trial.

The following adverse events are events of special interest:

* *[list of events]*

*Medical judgment should be performed to define these events. E.g. if an IMP is expected to have impact on liver function, laboratory deviations of liver enzymes might be an important safety signal.*

## Documentation and follow-up of adverse events

The sponsor ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject’s medical records and in the CRF.

*For the procedure of SAE-reporting see section 7.2.2 and section 4.8.1.3 for safety analyses.*

### Documentation of adverse events and adverse drug reactions

All AEs will be documented in the CRF including all information listed below.

AEs occurring within the following time frame will be documented:

*between first intake of IMP and 30 days after last dose of the individual subject.*

The AE is documented in the CRF including the following information:

* AE verbatim
* Date and time of onset and resolution
* Severity
* Causal relationship with IMP / study treatment
* Seriousness
* Action taken
* Outcome

Regardless of whether a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, *or the study has been terminated for the trial subject concerned*.

*Follow-up observation periods should be defined here (e.g. 30 days after the study is completed in the subject is generally used; see also 7.1.1). The duration of the follow-up observation period should be justified and based on known parameters of the IMP’s pharmacokinetics.*

* + - 1. *Exceptions from AE documentation*

*Exceptions can be described at this point, with reasons why they do not have to be documented in the CRF or are not classified as AEs in this clinical trial. Examples are changes in laboratory values that can be expected as part of the underlying disease (e.g. in oncological indications), and which would only have to be reported as AEs from a defined toxicity level upwards. Permitting such AEs not to be documented in the CRF does not free the investigator from any associated legal reporting requirements.*

Preexisting diseases (before administration of the IMP) are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

### Severity of the adverse event

The investigator will classify the severity of AEs as follows:

1. Mild: clinical symptoms or signs that are well tolerated
2. Moderate: clinical symptoms or signs that are enough to impair everyday activities
3. Severe: clinical symptoms or signs that markedly impair the trial subject and result in inability to work or go about everyday activities

*If established systems of classifications are to be used, such as the National Cancer Institute Common Toxicity Criteria, this should be mentioned here.*

*The terms use here must be the same as those used in the CRF. The categories used for the rating of severity and causality (see Section 7.2.3) should therefore be described using the terms that appear in the CRF.*

*Caution: ‘Severity’ should not be confused with the concept of ‘seriousness’ (see Section 7.1.3) used to differentiate between an AE and an SAE.*

### Causal relationship between adverse event and investigational medicinal product

The investigator will assess therefor every AE whether a causal relationship with the IMP and/or study procedure can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the IMP, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered due to lack of efficacy or as a symptom or sign of the underlying disorder, no causal relationship will be assumed.

Every AE will be assessed (eCRF/SAE-Report) according to the causality determinations of CIOMS VI-Group (Council for International Organizations of Medical Sciences) as follows:

* Related: There is a reasonable possibility that the AE may be related to the IMP
* Not related: There is not a reasonable possibility that the AE may be related to the IMP.

A report on an event which cannot be judged because information is insufficient or contradictory or has not been judeged will be regarded as related.

*In double-blind trials, it should be borne in mind that the investigator has to assess causality as if the trial subjects had received the active substance / IMP under investigation / experimental treatment (unless the trial subject’s treatment was unblinded for medical emergency reasons).*

*The following remarks might be helpful for the judgement for relatedness:*

*Related:*

* *A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.*
* *A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
* *A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.*
* *A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.*
* *A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.*

*Unrelated:*

* *A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.*

## Reporting of serious adverse events, adverse events of special interest, pregnancy and changes in risk-benefit assessment

Regardless of the assumed causal relationship, every SAE and AESI that occurs from the time of IMP administration *[or from the time when informed consent is obtained]* until the last visit *[longer, but no shorter time periods might be defined]* must be documented in the appropriate part of the CRF and reported on an SAE/AESI form to the sponsor. Pregnancies must be documented on separate pregnancy forms and reported to the sponsor within the defined periods (see Section 7.3.1.).

*It is advisable to give details of trial-specific processes for safety management, such as information and communication pathways, interfaces and clarification of responsibilities (contact persons, involvement of the DMC etc.) in a trial-specific manual. This section should refer to such a manual. A flowchart with reporting pathways and details of timing of reporting should also be prepared.*

*If safety documentation and reporting is being managed by a third-party, the entire Section 7.3 text should be adapted accordingly.*

### Reports from the investigator to the sponsor

*The investigator will inform the sponsor of the occurrence or receipt of knowledge of the occurrence of an SAE and any adverse event of special interest (AESI) without delay, at the latest within 24 hours of being made aware of the SAE/AESI.*

Contact details: xxx
Fax: xxx

*The following events will be documented in the CRF, but are not subject to expedited reporting:*

* *xxx.*

*Events may be excluded from the 24-hour reporting restriction, e.g. hospitalisation for planned chemotherapy for the underlying disease in an oncology trial unless it exceeds the planned duration. Nevertheless, they have to be documented in the CRF.*

*The investigator will also inform the sponsor without delay within 24 hours of being made aware of any pregnancy of a trial subject* [or its pregnant female partner] *that occurs during the trial and its outcome. This will be documented on the appropriate separate pregnancy forms. The pregnant trial subject will be asked to give separate informed consent for pregnancy follow up. The parents will be asked to give informed consent to follow-up of the child until 4 weeks after life birth.*

*The period for follow-up after life birth should be defined. If pharmacological characteristics of the IMP mean that it is necessary to document and follow up pregnancies in partners of male trial subjects, this should be described here. This is especially the case if the IMP is excreted in relevant concentrations in semen or if it is known to cause genetic defects.*

### Assessment of SAEs by the sponsor

*All cases of suspected SAEs are assessed by the sponsor* [the institution to which this task has been delegated should be named] *with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator’s assessments.*

### Unblinding for SUSAR when treatment is blinded

*For SUSARs* (in double-blind trials), *the trial treatment is unblinded by the sponsor in the individual trial subject to verify causality before reporting the event to the ethics committee and the competent authority.*

*The responsible competent authority should be entered into the text below if necessary.*

*This means that the trial subject’s treatment is unblinded and the potential SUSARs is reassessed, to decide whether there really is an at least possible causal relationship and whether the event should therefore be classified as a SUSAR. The procedure for causality assessment and unblinding and for the sponsor’s assessment should either be described in this section of the trial protocol or in other trial documents (e.g. manuals; if so, insert a reference).*

*If the trial has a data monitoring committee (DMC), the DMC may also be assigned tasks in unblinding (e.g. in the case of a potential SUSAR), to ensure that blinding for the sponsor and the trial team is maintained.*

*If a DMC is involved in unblinding, the responsibilities, the unblinding procedure, the communication pathways and reporting deadlines must be described in detail in the DMC charta for the DMC and appropriate manuals / SOPs for the sponsor before the study initiation (see also Section 3.4).*

### Notification of ethics committee and competent authority

*Every SUSAR that becomes known in a clinical trial will be reported by the sponsor to the competent authority and the ethics committee.*

*Reporting responsibilities and deadlines in other countries have to be respected in multinational trials (authorities, ethics committees and other bodies as required).*

*All reporting requirements are regulated in the appropriate document (manual or SOP).*

Fatal and life-threatening SUSARs

*The competent authority and the responsible ethics committee must be informed by the sponsor of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts will be made to obtain further relevant information which will be supplied to the competent authority and the ethics committee within a further 8 days.*

SUSARs that are not fatal or life-threatening

*The competent authority and the responsible ethics committee will be informed without delay by the sponsor of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.*

*If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.*

### Review and reporting of changes in the risk-benefit ratio

*The sponsor will inform the competent authority, the responsible ethics committee and the competent authorities of all other member states of the EU or EEA where the trial is being conducted, of any events or factors that mean that the risk-benefit ratio of the IMP has to be reviewed. This will be done without delay, at the latest within 15 days. This includes, but is not restricted to:*

* Individual reports of expected SARs with an unexpected outcome
* A clinically relevant increase in the rate of occurrence of expected SARs
* SUSARs in trial subjects who have already completed the follow-up period of the clinical trial (”end-of-trial visit”)
* Events in connection with the conduct of the study or the development of the investigational medicinal product which may affect the safety of the trial subjects.

### Informing the Data Monitoring Committee

*The DMC will be informed of all safety-relevant events by the sponsor.*

*Describe whether the DMC will be involved and, if so, details of the information they will receive (e.g. all SAEs, selected SAEs, SUSARs, and all other events of special interest). The details should be described in safety manuals, for the DMC or in similar documents and references to such documents should be made here (see also Section 3.4).*

### Informing the investigators

*The sponsor will inform investigators of all SUSARs in blinded form including all relevant further information within the periods set by the competent authority.*

*“blinded form” should be omitted in non-blinded trials.*

*The sponsor will inform all investigators on any change of information concerning the scientific documents of the trial (SmPC, Investigator’s Brochure, risk-benefit-ratio).*

### Informing the marketing authorisation holder

*The sponsor will also inform the marketing authorization holder about all SUSARs including information reported to the competent authority and ethics committee in accordance with contractual agreements.*

*Additional reporting requirements should be the subject of a separate contractual agreement and should be mentioned here accordingly.*

## Annual safety report (DSUR)

*The sponsor will supply annually a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent authorities of all concerned member states of the EU or EEA. This report will also be supplied to the responsible ethics committee.*

*The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“.*

*The sponsor will supply the report within 60 days after the reference date (data-lock point). The start of the annual period for the DSUR is the month and date of the DIBD. The data lock point of the DSUR should be the last day of the one-year reporting period.*

*The data lock point for the patient data to be included and analysed is defind by*

*- the “Development International Birth Date” (DIBD) of the study drug.*

*alternatively*

*- by the first approval of the clinical trial in the EU.*

*The DSUR presents a comprehensive analysis of the current safety profile concerning the study drug(s). The data lock point is the last day of the one-year reporting period following the “Development International Birth Date” (DIBD). This date is the sponsor’s first authorisation concerning the study drug, to conduct a clinical trial in any country worldwide. When the DIBD is not available to the sponsor, because of a multi-drug trial and/or an Investigator initiated trial, the DIBD can be defined as the first authorisation to conduct a clinical trial in the EU. An adequate explanation should be provided within the report. When clinical development of a drug continues following a marketing approval in any country worldwide, both a PSUR and a DSUR should be submitted as specified by national or regional laws or regulations. If desired by the sponsor, a DSUR can be prepared based on the PSUR International Birth Date (IBD) so that the DSUR and the PSUR can be synchronised. In synchronising the data lock points for the DSUR and PSUR, the period covered by the next DSUR should be no longer than one year.*

# Trial results and publication

## Reports

### Interim reports

Section 7.4 describes the requirements for annual reports on the safety of trial subjects.

If appropriate, describe reports that will be made to trial sponsors about progress of recruitment, interim reports etc.

### Final report

The competent authority and ethics committee will be informed within 90 days after the end of the trial as defined in 4.1.1.

Within one year after the end of the trial, the competent authority and the ethics committee will be supplied with the fullfinal study report (competent authority) or the summary of the final study report (ethics committee).

## Publication

The trial will be registered in a public register in accordance with the recommendations of the ICMJE (see also Section 5.4).

Trial results will be published in a scientific journal and presented at congresses, in mutual agreement with the sponsor. The sponsor intends to publish the results of the clinical trial with all trial sites involved as one trial group. Prior to this publication, trial sites will not publish own results. However, in the event that there is no first publication by the sponsor within twelve months after submission of the final clinical trial report, the trial site and the principal investigator shall have the right to publish or present the results of the trial site’s and principal investigator’s activities. Any publication will follow the ‘Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors’ (ICMJE) [JAMA 1997;277(11):927-34]).

Any publication will observe privacy concerning trial subjects and principal investigators. Success rates or individual findings of individual trial sites will not be disclosed by publications.

If necessary, this section should be used to list persons or bodies contracted by the sponsor who will receive data and will therefore be informed about the trial results.

Publications of trial results must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication. However, the sponsor will not withhold publication for non-scientific reasons.

By signing the contract to participate in this trial, the principal investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes. At the same time, the principal investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be disclosed to these bodies.

In case the CTCC and or IMSB are involved in the clinical trial, the following has to be adhered to:

The support by the CTCC / IMSB is to be mentioned in any publication. CTCC / IMSB staff will be included as coauthors as applicable. A copy of all publications will be sent to the CTCC. Respective procedures and arrangements will be detailed in the contract with the CTCC / IMSB.

# Amendments to the trial protocol

Changes to this trial protocol may only be implemented if agreed by the sponsor, sponsor’s representative, the PCI and statistician. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by the sponsor’s representative, the PCI and the statistician.

Significant changes will be implemented after approval by the competent authority and favourable opinion of the ethics committee, only. Exceptions to this are amendments made to avoid immediate dangers.

# References

1. The European Medicines Agnency. Guideline for Good Clinical Practice; (ICH Topic E6(R2)) (EMA/CHMP/ICH/135/1995).
2. The European Medicines Agnency. Note for Guidance on Structure and Content of Clinical Study Reports; (ICH Topic E3) (CPMP/ICH/137/95).
3. National Cancer Institute. Protocol Templates, Applications and Guidelines <http://ctep.cancer.gov/guidelines/templates.html>
4. EMEA-Guideline On Data Monitoring Committees: EMEA/CHMP/EWP/5872/03 Corr
5. The DAMOCLES Study Group. A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well. Lancet 2005; 365: 711-22
6. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Accessed on 22 May 2007 at <http://www.icmje.org/clin_trial.pdf>.
7. WHO - Standardised case causality assessment. <http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf>
8. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj. 2013;346:e7586.
9. The European Medicines Agnency. Note for Guidance on Statistical Principles for Clinical Trials; (ICH Topic E9) (CPMP/ICH/363/96) <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/statistical-principles-for-clinical-trials.html>.
10. Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors’ (ICMJE) [JAMA 1997;277:927-34].

# Appendices *(to be adapted)*

## Trial sites with principal investigator and deputy

## Protocol Agreement Form

## Steering Committee

## Data Monitoring Committee

## Advisory Committee

## Study laboratories and other technical resources

## Sample labels for investigational medicinalris product (IMP)

## Patient informed consent form

## Prescribing information

## Confirmation of insurance

## Conditions of insurance