

Drug Name/Code  
Triall Code  
CSR Date

## CLINICAL STUDY REPORT

< Title >

*Title should include name of investigational product(s), indication and essentials of study design. If this information is not present in the title it should be added to the list below.*

Protocol Code	
ClinicalTrials.gov registry number	
EudraCT Number	
Sponsor	
Phase	
First patient enrolled	
Last patient completed	
Clinical Study Coordinator	
Report Date	

This study was conducted in accordance with protocol, Good Clinical Practice ICH Topic E6 (R2) and applicable regulation. This document is sole property and ownership of the Sponsor. All data and information contained herein has to be considered and treated as confidential and no disclosure or publication shall be made without prior written consent of the Sponsor.

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## SINOPSYS

*A brief synopsis (usually limited to 3 pages) that summarises the study should be provided. The synopsis should include numerical data to illustrate results, not just text or p-values.*

<b>Name of Sponsor:</b>	<b>Investigational Product:</b>
<b>Protocol Code:</b>	<b>Phase of Development</b>
<b>Title of the study:</b>	
<b>Coordinating Investigator:</b>	<b>Study Period:</b> <i>Date first patient enrolled – Date last patient enrolled</i>
<b>Study sites</b>	
<b>Objectives</b> <u>Primary</u> <u>Secondary</u>	
<b>Study design and methodology</b>	
<b>Subject population</b> <i>Number of Subjects planned</i> <i>Number of subjects enrolled</i> <i>Number of Subjects randomized (if applicable)</i> <i>Number of subjects for each analysis population</i>  <i>Brief description of demographic and baseline characteristics</i> <i>Brief description of subjects excluded from primary analysis population</i>	

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## Eligibility Criteria

## Study products / Dose and Mode of administration/Duration of treatment/interventions

*Describe test and reference products / interventions*

## Duration of Treatment

## Study Endpoints

## Statistical methods

## Summary of results

Efficacy results

Safety results

## Conclusions

## Date of the report

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## 1. ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
EC	Ethics Committee
GCP	Good Clinical Practice
ISF	Investigator Site File
PI	Principal Investigator
SAE	Serious Adverse Event
TMF	Trial Master File

## 2. ETHICS

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with the International Conference on Harmonization Guidelines for Good Clinical Practice (GCP).

The study was reviewed and approved by the competent Ethics Committee (EC) of each participating site and by the Regulatory Authority of each involved Country.

The approved Clinical Study Protocol and protocol amendment(s) is / are presented in Appendix XX, and the list of the consulted ECs in Appendix XX.

EC and Regulatory Authority approvals were filed centrally and locally in the Trial Master File (TMF) and Investigator's File (ISF), respectively, as required by GCP.

The submitted documentation included the patient information sheet and informed consent form.

The consent to participate in the study was obtained in writing from all patients (or patient's acceptable representative), prior to inclusion in the trial and after an adequate verbal and written full explanation regarding the objective and procedures of the trial and the possible risks involved. The consent form was to be personally signed and dated by the patient/legal representative and by the investigator conducting the informed consent procedure.

Patient information sheets and informed consent forms were prepared by the Principal Investigator (PI) of each institution following local regulatory and ethical requirements; these documents, including any subsequent revisions, were submitted and approved by the competent EC before their use. The right of a patient to refuse to participate or withdraw at any time from protocol treatment without giving reasons and without prejudicing further treatment was respected. A sample of the patient information sheet(s)/informed consent form(s) is provided in Appendix XX.

The clinician remained free to give alternative treatment to that specified in the protocol at any stage if it was in the patient's best interest.

A clinical trial-specific liability insurance was stipulated.

## 3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

*The administrative structure of the study (e.g. coordinating investigator, steering committee, monitoring and evaluation committees, institutions, statistician, central laboratory facilities, contract research organisation (C.R.O.), clinical trial supply management, participating institutions and relevant Principal Investigators) should be described briefly.*

*If there are several participating institutions to be listed, they can be included as an appendix.*

Appendix XX lists the investigators and their affiliations. Appendix XX contains the signature of the Principal Investigator(s).

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## 4. INTRODUCTION

*The introduction should contain a brief statement (approximately 1 page) placing the study in the context of the development of the investigational treatment, relating the critical features of the study (e.g., rationale and aims, target population, treatment, duration, primary endpoints) to that development.*

## 5. OBJECTIVES AND ENDPOINTS

*Describe the primary and secondary study objectives.*

*Provide secondary objectives as numbered items and ensure consistency with endpoints/outcomes, i.e., the correspondence between each objective and the relevant measurement parameters must be clear.*

### 5.1. Objectives

5.1.1 Primary Objective

5.1.2 Secondary Objectives

### 5.2. Endpoints

5.2.1 Primary Endpoint

5.2.2 Secondary Endpoints

## 6. INVESTIGATIONAL PLAN

### 6.1. Overall Study Design and Plan

*The overall study plan and design (e.g., parallel, cross-over) should be described briefly but clearly, using charts and diagrams as needed.*

*The information provided should include:*

- *treatments studied (specific drugs, doses and procedures);*
- *patient population studied and the number of patients to be included;*
- *kind of control(s) (e.g., placebo, no treatment, active drug, dose-response, historical) and study configuration (parallel, cross-over);*
- *method of assignment to treatment (randomisation, stratification);*
- *sequence and duration of all study periods, including pre-randomisation and post-treatment periods, therapy withdrawal periods. When patients are randomised should be specified. It is usually helpful to display the design graphically with a flow chart which includes timing of assessments (see Annexes IIIa and IIIb for an example);*
- *any safety, data monitoring or special steering or evaluation committees;*
- *any interim analyses.*

### 6.2. Discussion of Study Design

*The specific control chosen and the study design used should be discussed, if appropriate.*

*Examples of design issues meriting discussion:*

- *Known or potential problems associated with the study design or control group chosen, to be discussed in light of the specific disease and therapies being studied.*



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- *Pesence or absence of washout periods, duration of the treatment period, especially for a chronic illness.*
- *Rationale for dose and dose-interval selection to be explained, if it is not obvious.*

### 6.3. Selection of Study Population

*The patient population should be described, and the suitability of the population for the purposes of the study briefly stated.*

*Screening criteria and any additional criteria for randomisation or entry into the test drug/investigational product treatment part of the trial should be described.*

#### 6.3.1 Inclusion criteria

*Report selection criteria used to enter the patients into the study.*

*Specific diagnostic criteria used, as well as specific disease requirements (e.g., disease of a particular severity or duration, results of a particular test or rating scale(s) or physical examination, particular features of clinical history, such as failure or success on prior therapy, or other potential prognostic factors and any age, sex or ethnic factors) should be presented.*

#### 6.3.2 Exclusion criteria

*Report criteria for exclusion at entry into the study.*

*The impact of exclusions on the generalisability of the study should be discussed in the report under "Discussion and Overall Conclusions", or in an overview of safety and efficacy.*

#### 6.3.3 Removal of patients from therapy or assessment

*List the predetermined reasons for removing patients from therapy and/or from the study. For example:*

The study treatment was to be continued until any of the following occurred:

- Disease progression at any time;
- Unacceptable toxicity dictating cessation of treatment;
- Change in patient's conditions (including pregnancy) such that the Investigator believed that patient's safety might be compromised by treatment or that it was in the best interest of the patient to stop treatment;
- Withdrawal of consent; if a patient decided to discontinue completely his/her study participation and did not authorize the Sponsor to collect further information about his/her disease status, no further attempts were to be made to collect additional data;
- Non-compliance by the patient with protocol requirements
- Patient lost to follow-up; if a patient did not return for scheduled visits, every effort was to be made to re-establish contact. In any circumstance, every effort was to be made to document patient outcome.



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## 6.4. Treatments

### 6.4.1. Treatments Administered

*The precise treatments to be administered in each arm of the study, and for each period of the study, should be described including route and mode of administration, dose and dosage schedule.*

### 6.4.2. Identity of investigational product(s)

*Brief description of the test drug(s)/investigational product(s) (formulation, strength, route of administration).*

*If more than one batch of test drug/investigational product was used, refer to the drug accountability records archived in the TMF for the identification of patients receiving each batch.*

*Provide the source of placebos and active control/comparator product(s).*

*Describe specific storage requirements, if applicable.*

### 6.4.3. Method of Assigning Patients to Treatment Groups

*Describe the specific methods used to assign patients to treatment groups, e.g., centralised allocation, allocation within sites, adaptive allocation, including any stratification or blocking procedures.*

*Explain the method of generating random numbers.*

*For a historically controlled trial, it is important to explain how the particular control was selected and what other historical experiences were examined, if any, and how their results compared to the control used.*

### 6.4.4. Selection and timing of doses in the study

*Provide doses or dose ranges used in the study for all treatments and the basis for choosing them.*

*If appropriate, describe procedures for selecting each patient's dose (e.g., random assignment or titration procedures used in dose escalation/dose finding studies; procedures for de-escalation/dose reduction should also be described).*

*If applicable, describe the timing (time of day, interval) of dosing and the relation of dosing to meals and specify what kind of instructions were provided to patients about when or how to take the dose(s).*

### 6.4.5. Prior and Concomitant Therapy

*Which drugs or procedures were allowed/required before and during the study, whether and how their use was recorded, and any other specific rules and procedures related to permitted/required or forbidden concomitant therapy.*

*Provide a rationale for requiring or forbidding specific therapies.*

*The following text can be reported if applicable:*

All concomitant medications had to be entered into the CRF. Therapies considered necessary for the patient's well being could be given at the discretion of the Investigator, i.e. chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, analgesics etc. Patients were to be advised to contact the treating physician before starting any new treatment.

### 6.4.6. Treatment compliance

*Report the following text if applicable:*

Records of study medication used, actual and total doses administered, dose modifications, delays and omissions, as well as reasons for deviation from planned therapy were to be kept during the study and recorded in the CRF.

*In addition, describe other measures taken to ensure and document treatment compliance (e.g.,*

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*drug accountability records, unused drug counting during monitoring visits, patient diaries).*

## 6.5. Efficacy and Safety Variables and Measurement Procedures

*Adapt the order of sections 6.5.2 and 6.5.3 to the corresponding objectives: first describe the variables relevant to the primary objective and then those relevant to the secondary objectives. Ensure correspondence between each objective and the relevant efficacy/safety variables, preferably by using numbered items.*

*Any definitions used to characterise outcome (e.g., criteria for determining tumor response, definition of adverse event and classification of severity, seriousness, causality) should be explained in full.*

*Any techniques used to standardise or compare results of laboratory tests or other clinical measurements should also be described.*

*If anyone other than the investigator was responsible for evaluation of clinical outcomes (e.g., the sponsor or an external committee) the person or group should be identified. The procedures, and centralising readings and measurements, should be described fully.*

### 6.5.1. Study Flow Chart

Planned assessments and study procedures are summarized in Table/Figure XX:

### SCHEDULE OF EVENTS / FLOWCHART

*If the primary objective is an efficacy objective, describe the efficacy variables first; if the primary objective is a safety objective, describe the safety variables first.*

### 6.5.2. Efficacy Variable(s)

### 6.5.3. Safety Variable(s)

*The means of obtaining adverse event data should be described (volunteered, checklist, questioning, clinical, instrumental, laboratory examinations).*

*Provide definitions and criteria for Adverse Event, Serious Adverse Event, exposure in utero, AE severity grading and causality assessment, as described in the study protocol.*

*Describe procedures for AEs/SAEs/pregnancies reporting and mention any exceptions to the standard procedures foreseen by protocol (e.g., events fulfilling the SAE definition, which were not to be reported as such).*

*Describe timing and duration of follow-up procedures.*

*Here below is an example:*

#### Adverse Events

An AE was defined as any untoward medical occurrence in a patient or a clinical trial subject administered a medicinal product and which did not necessarily have causal relationship with the use of the product. An adverse event could therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or diagnosis temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any untoward medical occurrence, which occurred outside the period of subject follow-up defined in the protocol, was not considered an AE. Symptoms or medically significant laboratory or instrumental (e.g., by electrocardiography) abnormalities of a pre-existing condition had not to be considered an AE. However, occurrence of new symptoms, laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, were to be considered AEs.

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### *Tumor progression*

*In this trial, the general concept of “tumor progression” had not to be reported as an adverse event, while the specific symptoms of disease worsening (if any) had to be reported as adverse events.*

*The criteria applied for laboratory abnormalities reporting in the AE section of the CRF should be clarified. For example, if abnormal results were to be reported as AEs only when considered clinically significant and specific criteria were provided to define clinical significance, these should be described. For example:*

### **Abnormal Laboratory Findings**

Any abnormal laboratory findings of Grade  $\geq$ X, including uncomplicated and asymptomatic abnormal laboratory findings, were to be considered adverse events and were to be collected, graded, and reported in the CRF. In addition, laboratory abnormalities fulfilling the SAE criteria or requiring any action such as study treatment modifications or therapeutic measures, were also to be considered as adverse events.

### **Serious Adverse Events**

An adverse event that met one or more of the following criteria/outcome was classified as serious:

- Resulting in death
- Life-threatening, i.e., an event which, in the view of the Investigator, places the subject at immediate risk of death from the event as it occurred (it does not include an event which hypothetically might have caused death if it were more severe)
- Requiring inpatient hospitalization or prolongation of existing hospitalization
- Resulting in persistent or significant disability/incapacity, where disability was defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment
- Was a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child)
- Any other important medical event, that could not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment, it could jeopardize the subject and could require medical or surgical intervention to prevent one of the outcomes listed in the points above. A non-serious adverse event was any adverse event that did not meet the criteria listed above or the outcome could not be determined with the information provided.

### **Reporting Procedures**

The AE/SAE reporting period began upon signing of informed consent and ended after XX.

All AEs/SAEs occurred to the patients during the reporting period had to be reported to the Sponsor, whether or not the event was considered related to the study medication. In addition, any known SAE suspected to be related to the study treatment occurring after the defined reporting period, had also to be reported to the Sponsor.

### **Exposure In Utero**

In case of exposure in utero (including pregnancy occurring within xx days of discontinuing test therapy) the Investigator had to submit this information on an Exposure in Utero Form within 24 hours of awareness of the pregnancy. The Investigator had to follow the subject until completion of the pregnancy and notify of the outcome. Spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus, were to be classified as SAEs and reported following the procedures for SAE reporting.

### **Recording Adverse Events in the Case Report Forms**

All AEs and SAEs were to be reported on the CRF and the relationship between the adverse event and the investigational medication was to be assessed by the Investigator. Each adverse event had to be reported

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once for cycle, at the worst CTC grade/All changes in AE severity within a cycle were to be recorded in the CRF and if an event stopped and later restarted within the same cycle, all the occurrences had to be reported.

### Grading of Adverse Event Severity

In this study the severity of the adverse events was to be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version X.0 of the US National Cancer Institute.

### Relationship to the Study Treatment

The causal relationship between each AE/SAE and the study treatment had to be classified according to the following categories: xxx, xxx, xxx.

### Coding of Adverse Events

All AEs were coded by the Sponsor at the Lower Level Term (LLT) according to the Medical Dictionary for Regulatory Activities (MedDRA) Version XX.

*Describe also how other safety parameters were to be collected and evaluated, in particular how abnormal laboratory findings or were to be handled.*

#### 6.5.4. Drug Concentration Measurements

*If the protocol included pharmacokinetic assessments, describe concentrations to be measured, and the sample collection times and periods in relation to the timing of drug administration. Any relation of drug administration and sampling to ingestion of food, posture and the possible effects of concomitant medication/alcohol/caffeine/nicotine should also be addressed, if appropriate. Specify the type of biological sample measured (e.g., plasma, urine), the handling of samples and the method of measurement, referring to published and/or internal assay validation documentation for methodological details.*

#### 6.5.5. Appropriateness of Measurements

*If any of the efficacy or safety assessments was not standard, its reliability, accuracy and relevance should be documented.*

*If a surrogate end point (a laboratory measurement or physical measurement or sign that is not a direct measure of clinical benefit) was used as a study end point, this should be justified e.g., by reference to clinical data, publications, guidelines or previous actions by regulatory authorities.*

### 6.6. Data Quality Assurance

*Quality assurance and quality control systems implemented to assure the quality of the data.*

*Any steps taken at the investigational site or centrally to ensure the collection of accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, use of a central laboratory for certain tests, centralised ECG/radiological images reading, should be described.*

*If the sponsor used an independent internal or external auditing procedure, it should be mentioned here and audit certificates, if available, should be provided as an Appendix.*

The trial sites might have been also subject to review by the competent Ethics Committees, to quality assurance audits performed by the Sponsor and/or to inspection by regulatory authorities. For this purpose the investigator/institution had to guarantee direct access to source documents to auditors and inspectors.

Audit/inspection certificates, are provided in Appendix XX.



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## 6.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

### 6.7.1. Statistical and Analytical Plans

*Describe the statistical analyses planned in the protocol, not those that were actually performed. If a Statistical Analysis Plan is available, it should be included in Appendix XX and reference can be made to this document for non essential details.*

*Specify if according to protocol any patients were to be excluded from analysis populations. If there were any subgroups whose results were to be examined separately, these should be identified. If categorical responses (scales, severity scores, responses of a certain size) were to be used in analysing responses, they should be clearly defined.*

*If there was a data monitoring committee, either within or outside the sponsor's control, its composition and operating procedures should be described. Also describe frequency and nature of any planned interim analysis, any specified circumstances in which the study would be terminated and any statistical adjustments to be employed because of interim analyses.*

### 6.7.2. Determination of Sample Size

*Provide the planned sample size and the basis for it, such as statistical considerations or practical limitations. Methods for sample size calculation should be given together with their derivations or source of reference. Estimates used in the calculations should be given and explanations provided as to how they were obtained. For a study intended to show a difference between treatments, the difference the study is designed to detect should be specified.*

## 6.8. Changes in the Conduct of the Study or Planned Analyses

*Any change in the conduct of the study or planned analyses (e.g., changing the entry criteria or drug dosages, adjusting the sample size etc.) instituted after the start of the study should be described. The time(s) and reason(s) for the change(s) should also be described, whether the change was documented as a formal protocol amendment or not (personnel changes need not be included).*

*Any possible implications of the change(s) for the interpretation of the study should be discussed briefly in this section and more fully in other appropriate sections of the report.*

*In every section of the report, a clear distinction between conditions (procedures) planned in the protocol and amendments or additions should be made.*

### 6.8.1. Protocol amendments

### 6.8.2. Changes in the Statistical Plan

## 7. STUDY PATIENTS

*All results presented in Sections 7-10 should cross-reference the corresponding source tables/figures included in Section 13. For example:*

*[Source: Section 13, Table XX]*

### 7.1. Disposition of Patients

*There should be a clear accounting of all patients who entered the study, using figures or tables. The numbers of patients who were enrolled/randomised, and who entered and completed each phase of the study, should be provided, as well as the reasons for all discontinuations, grouped by treatment and by major reason (lost to follow-up, adverse event, poor compliance etc.). It may also be relevant to provide the number of patients screened for inclusion and a breakdown of the reasons for excluding patients during screening, if this could help clarify the appropriate patient population for eventual drug use. A flow chart is often helpful. Whether patients are followed for the*

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*duration of the study, even if drug is discontinued, should be made clear.  
The following is an example of how patient disposition can be summarized:*

A summary of patient disposition and reasons for withdrawal from treatment and ending study is provided in TableXX

**Table XX. Patient Disposition**

	Group A		Group B		Overall	
	n	%	n	%	n	%
<b>Patient Enrolment and Treatment</b>						
Screened						
Enrolled						
Randomized						
Treated						
Completing Study Treatment						
<b>Reason for Treatment Withdrawal</b>						
Treatment completed as per protocol						
Tumor Progression						
Adverse Event						
IMP-related						
IMP-unrelated						
Consent Withdrawal						
Lack of compliance						
Other						
<b>Total off treatment</b>						
<b>Reason for Ending Study</b>						
Follow up completed as per protocol						
Lost to Follow up						
Start of new therapy						
Death						
Other						
<b>Total off study</b>						

## 7.2. Protocol Deviations

*All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described.*

*Protocol deviations should be summarised and grouped into different categories, such as:*

- those who entered the study even though they did not satisfy the entry criteria;*
- those who developed withdrawal criteria during the study but were not withdrawn;*
- those who received the wrong treatment or incorrect dose;*
- those who received an excluded concomitant treatment.*

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### 7.3. Demographic and Other Baseline Characteristics

*Group data for the critical demographic and baseline characteristics of the patients, as well as other factors that could affect response, should be presented and comparability of the treatment groups for all relevant characteristics should be displayed.*

*The data for all patients should be given first and this can then be followed by data on other sub-populations used in the analyses, such as the "per-protocol" analysis.*

*The critical variables will depend on the specific nature of the disease and on the protocol but will usually include:*

*demographic variables*

- age*
- sex*
- race*
- disease factors*
  - specific entry criteria (if not uniform), duration, stage and severity of disease and other clinical classifications and sub-groupings in common usage or of known prognostic significance*
  - baseline values for critical clinical measurements carried out during the study or identified as important indicators of prognosis or response to therapy*
  - previous and concomitant illnesses at trial initiation*
  - relevant previous treatment for illness treated in the study*
  - concomitant treatment at trial initiation*

*other factors that might affect response to therapy (e.g., genetic characteristics)*

*other possibly relevant variables (e.g., women's menopausal status, if pertinent for the study).*



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**Table XX. Demographic and other Baseline Characteristics (Treated Patients)**

	Group A		Group B		Overall	
	N=		N=		N=	
	n	%	n	%	n	%
<b>Age (yrs)</b>						
Median						
(range)						
< XX – yrs						
≥ XX – yrs						
<b>Sex</b>						
Female						
Male						
<b>BSA (m2)</b>						
Mean						
(range)						
<b>Performance status (ECOG)</b>						
0						
1						

#### 7.4. Data Sets Analysed

*Analysis populations must be defined, e.g., which patients were included in the intention-to-treat analysis (e.g., all patients receiving at least one IMP dose, even if not receiving the correct treatment according to randomization), which ones in the per-protocol efficacy analysis (e.g., all patients with no major eligibility violations and undergoing at least one on-treatment assessment), which ones in the safety analysis, etc.*

*It must be specified which data set was used for the primary analysis. Even if the primary analysis is based on a reduced subset of the patients, there should also be for any trial intended to establish efficacy an additional analysis using all randomised (or otherwise enrolled) patients with any on-treatment data.*

*A listing of patients excluded from the primary analysis should be provided as an Appendix.*

*Here below is an example of table that can be used to summarize the analysis populations:*

**Table XX. Analysis populations**

	Group A	Group B	Overall
<b>Enrolled</b>			
<b>Treated</b>			
<b>Intention-to-treat Population</b>			
<b>Per-protocol (Efficacy-evaluable) Population</b>			
<b>Safety-evaluable Population</b>			

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## 8. MEASUREMENTS OF TREATMENT COMPLIANCE AND EXPOSURE

### 8.1. Treatment Compliance

*Measurements of compliance with the treatment regimen under study summarised and analysed by treatment group.*

*Treatment compliance is intended as the degree of conformity with respect to doses and schedules defined in the protocol. Dose delays, reductions and withdrawals performed according to protocol instructions should not be considered as non-compliance, while wrong drug intake/administration (e.g., not corresponding to the randomization arm the patient was assigned to), significant dosing errors (e.g., >10%), delays and interruptions not required by protocol, should be considered as lack of compliance.*

*Non-compliance can affect efficacy and safety results; for this reason, in case of unexpected findings, it might be useful making reference to treatment compliance when describing safety and efficacy results.*

### 8.2. Treatment Exposure

*The extent of exposure should be characterised in terms of number of patients exposed, duration of exposure, and dose to which they were exposed.*

*Duration: Duration of exposure to any dose can be expressed as a median or mean, but is also helpful to describe the number of patients exposed for specified periods of time (e.g., in case of cyclical treatments: 1-2 cycles, 3-4 cycles, 4-6 cycles, etc. or in case of continuous treatments: 1-60 days, 61-90 days, 91-120 days, etc.)*

*Dose: The mean or median dose used and the number of patients exposed to specified dose levels should be given.*

*It is often useful to provide combined dose-duration information, such as the absolute and relative weekly dose intensity.*

## 9. EFFICACY EVALUATION

*Sections 8 and 9 should be reversed if safety is the primary objective.*

### 9.1. Analysis of Efficacy

*The analysis should fulfill the study objectives and be based on the efficacy variables described in section 6.5.1.*

*If the analysis includes comparisons between groups, it should show the size (point estimate) of the difference between groups, the associated confidence interval, and where utilised, the results of hypothesis testing.*

*If categories are newly created, (i.e., not in the statistical plan) the basis for them should be explained.*

*If any critical measurements or assessments were made by more than one party (e.g., both the investigator and an independent reviewer assessed tumor responses), overall differences between the ratings should be shown, and each patient having disparate assessments should be identified. The assessments used should be clear in all analyses.*

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### 9.1.1. Statistical/Analytical Issues

*Important features of the analysis including the particular methods used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of drop-outs and missing data, adjustments for multiple comparisons, special analyses of multicentre studies, and adjustments for interim analyses, should be discussed. In addition, other specific issues should be addressed if applicable, such as:*

### 9.1.2. Adjustments for Covariates

*Selection of, and adjustments for, demographic or baseline measurements, concomitant therapy, or any other covariate or prognostic factor should be explained in the report, and methods of adjustment, results of analyses, and supportive information (e.g., ANCOVA or Cox regression output) should be included in the detailed documentation of statistical methods. If the covariates or methods used in these analyses differed from those planned in the protocol, the differences should be explained and where possible and relevant, the results of planned analyses should also be presented.*

### 9.1.3. Handling of Dropouts or Missing Data

*Dropout rates may be affected by various factors, such as the duration of the study, the nature of the disease, the efficacy and toxicity of the drug under study, and other factors that are not therapy related. Drawing conclusions based only on patients who completed the study can be misleading but including dropouts in an analysis, may introduce bias. In trials where the possible effects of dropouts are considered, the approaches used to the evaluation of such incomplete data sets should be described.*

*Procedures for dealing with missing data, e.g., use of estimated or derived data, should be described. Detailed explanation should be provided as to how such estimations or derivations were done and what underlying assumptions were made.*

### 9.1.4. Interim Analyses and Data Monitoring

*Interim analyses can introduce bias and/or increase type I error if the code is broken. Therefore, all interim analyses, formal or informal, pre-planned or ad hoc, by any study participant, sponsor staff member, or data monitoring group should be described in full, even if the treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed.*

*The outcome of any data monitoring meeting that led to protocol changes or early termination of the study should be described.*

### 9.1.5. Multiple Comparison/Multiplicity

*False positive findings increase in number as the number of significance tests (number of comparisons) performed increases. If there was more than one primary endpoint (outcome variable), more than one analysis of particular endpoint, or if there were multiple treatment groups, or subsets of the patient population being examined, provide the statistical adjustment used for type I error criteria or give the reasons why it was considered unnecessary.*

### 9.1.6. Tabulation of Individual Response Data

*In addition to tables and graphs representing group data, individual response data and other relevant study information should be presented in listings if appropriate.*

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### 9.1.7. Drug Dose, Drug Concentration, and Relationships to Response

*If appropriate provide information on dose-response relation.*

*Drug concentration information, if available, should also be provided in pharmacokinetic terms and, if possible, related to response.*

## 9.2. Efficacy Conclusions

*The important conclusions concerning efficacy should be concisely described, considering primary and secondary end points.*

## 10. SAFETY EVALUATION

*It is assumed that all patients entered into treatment who received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.*

### 10.1. Adverse Events (AEs)

*An overall summary of the treatment-emergent AEs, i.e., of all events occurring or worsening after initiation of study treatments, should be displayed in a summary table, for example:*

**Table XX. Overall Summary of Treatment-Emergent Adverse Events (Treated Patients)**

	Number of patients		
	Group A	Group B	Overall
	N=	N=	N=
No. patients with at least one AE			
No. patients with at least one severe (CTCAE Grade $\geq 3$ ) AE			
No. patients with at least one SAE			

*A summary of the incidence of AEs should also be provided. If not all treatment-emergent AEs are presented, the selection of the most significant AEs should be based on considerations such as frequency and severity (for example, the table may display AEs with incidence > 5% and/or with severity Grade 3-4).*

*A separate table showing only the adverse events considered at least possibly related to drug use should also be included.*

*The tables should list each adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence. When treatments are cyclical, e.g., cancer chemotherapy, it may also be helpful to list results by cycle. Adverse events should be presented by MedDRA Primary Preferred Term (PPT) and grouped by System Organ Class (SOC). Each event may then be divided into defined severity categories according to the CTCAE scale used in the study.*

*Examples of such tabular presentations are provided here below.*

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**Table XX. Most common (overall frequency  $\geq$  XX%) Treatment-Emergent Adverse Events by MedDRA System Organ Class and Primary Preferred Term (Treated Patients)**

System Organ Class	Preferred Term	Group A		Group B		Overall	
		N=		N=		N=	
		n	%	n	%	n	%
XXX	XXX						
	XXX						
	XXX						
XXX	XXX						
	XXX						
	XXX						
XXX	XXX						
	XXX						
	XXX						

System Organ Class	Preferred Term	Group A				Group B				Overall			
		N=				N=				N=			
		Any G		G 3-4		Any G		G 3-4		Any G		G 3-4	
		n	%	n	%	n	%	n	%	n	%	n	%
XXX	XXX												
	XXX												
	XXX												
XXX	XXX												
	XXX												
	XXX												
XXX	XXX												
	XXX												
	XXX												

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All AEs for each patient are listed in appendix XX, including both the coded terms and the original terms used by the investigator, start and stop dates, severity, seriousness, actions taken, outcomes, and causality assessments.

## 10.2. Deaths, Serious Adverse Events, And Other Significant Adverse Events

### 10.2.1. Deaths

All deaths occurring during the study, including the post treatment follow-up period, and deaths that resulted from a process that began during the study, should be listed as in the example here below.

**Table XX. Patients who died**

Group	Pt. No.	Sex	Age (years)	Cycle No.	Days since First Dose	Days since Last Dose	Cause of Death	Comments
<b>A</b> (N= )								
<b>B</b> (N= )								

### 10.2.2. Serious Adverse Events

All serious adverse events should be summarized by patient in a listing format, as in the example below.

**Table XX. Serious Adverse Events (SAEs)**

Group	Pt. No.	Investigator Term	MedDRA Primary Preferred Term	Cycle No.	Seriousness criteria	Treatment-related (Y/N) Investigator	Treatment-related (Y/N) Sponsor	Outcome	Treatment withdrawal (Y/N)	SUSAR (Y/N)
<b>A</b> (N= )										
<b>B</b> (N= )										

SUSAR = Suspected Unexpected Serious Adverse Reaction



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*A comment should be provided for Suspected Unexpected Serious Adverse Reactions about the new safety findings' implications, if any.*

### 10.2.3. Other Significant Adverse Events

*Describe any events that led to a significant intervention, e.g., treatment withdrawal or dose reduction. These AEs can be summarized in a listing or table format as in the examples below.*

**Table XX. Adverse Events Causing Withdrawal from Study Treatment**

Group	Pt. No.	Cycle No.	MedDRA Primary Preferred Term	CTCAE Grade	Serious (Y/N)	Treatment-related (Y/N)
A (N= )						
B (N= )						

**Table XX. Adverse Events Requiring Dose Reduction**

[illegible]

#### 10.2.4. Narratives of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

*Brief narratives describing each death, each other serious adverse event, and those of the other significant adverse events that are judged to be of special interest because of clinical importance.*



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*Events that were clearly unrelated to the test drug/investigational product may be omitted or described very briefly. In general, the narrative should describe the following:*

*the nature and intensity of event, the clinical course leading up to event, with an indication of timing relevant to study treatment administration; relevant laboratory measurements, whether the drug was stopped, and when; countermeasures; post mortem findings; investigator's opinion on causality, and sponsor's opinion on causality and expectedness, if appropriate.*

*In addition, the following information should be included:*

- Patient identifier*
- Age and sex of patient; general clinical condition of patient, if appropriate*
- Disease being treated (if the same for all patients this is not required) with duration (of current episode) of illness*
- Relevant concomitant/previous illnesses with details of occurrence/duration*
- Relevant concomitant/previous medication with details of dosage*
- Study treatment administered, drug dose, and length of time administered.*

*Here below is an example of case narrative.*

**Patient # XXX**  
**Group A – XXX**

**Serious Adverse Events: Dyspnoea (MedDRA PPT: Dyspnoea), Pneumonia Right (MedDRA PPT: Pneumonia)**

This report concerned a 63 year-old female patient affected by breast cancer spread to lungs, spleen and bones, with a prior history of myocardial infarction, hysterectomy, and surgical treatment of varicose veins. The patient's concurrent diseases included allergic bronchial asthma, allergy to animal hair, pericardial and pleural effusion, hypertension, hepatomegaly, cholecystolithiasis. Symptoms at study entry were dyspnoea and fatigue.

The patient was enrolled in Group A and started XXX treatment on 20-Jul-2009 at a dose of 20 mg/day. Concomitant medications included olmesartan medoxomil for arterial hypertension, fluticasone and salmeterol for bronchial asthma, and colecalciferol and ibandronic acid for pain due to bone metastases. The study treatment was discontinued on 14-Aug-2009 (day 26 of cycle 1) due to stomatitis and developed severe dyspnoea on 23-Aug-2009. On 24-Aug-2009 the patient was admitted to the hospital with rapidly progressing dyspnea and right pneumonia was diagnosed by X-ray. She received dafalgan for pain, iv antibiotics (augmentin), and oxygen.

Blood test results were as follow: ...

On the following day (25-Aug-2009) C-reactive protein decreased to ... but no improvement of dyspnea was observed. There were no signs of thrombosis or bleeding. The patient was transferred to a medical ward on the same day, she refused intubation and died on 27-Aug-2009.

As per autopsy report, suppurating bronchial pneumonia and tumour metastases were present in the middle lobe of the right lung, which had led to severe tightening of the hilar tissue of the lung and adjacent mediastinal fatty tissue and pericardium.

The investigator reported dyspnea and right pneumonia as the cause of death and assessed their relationship to the study treatment as possible.

The Sponsor's assessment confirmed the suspected relationship between the reported events and the study treatment.

Pneumonia and dyspnea are expected based on the reference safety information.

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### 10.3. Clinical laboratory evaluation

*Laboratory test abnormalities should be graded according to the CTCAE criteria whenever possible. For tests not included in the CTCAE terminology, the results can be displayed as “low” (below the lower limit of normal), “normal” (within the normal range) and “high” (above the upper limit of normal) or by presenting mean or median values or by grouping abnormal of a certain size (e.g., twice the upper limit of normal, 5 times the upper limit; etc.).*

*Laboratory results can be presented as worst results by patient or by defined time intervals (e.g., by treatment cycle).*

#### 10.3.1. Individual Patient Changes

*An analysis of individual patient changes can be given if appropriate, e.g., using shift tables grouping the patients based on their baseline values (e.g., low, normal, high) and showing their worst change during treatment or for selected periods (e.g., by treatment cycle).*

### 10.4. Vital signs, physical findings and other observations related to safety

*Vital signs, other physical findings, and other observations related to safety should be analysed if appropriate and presented in a way similar to laboratory variables.*

### 10.5. Safety conclusions

*The overall safety evaluation of the investigational treatment(s) should be reviewed, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. The implication of the safety evaluation for the possible uses of the drug should be described.*

### 10.6. Discussion and overall conclusions

*The efficacy and safety results of the study and the relationship of risks and benefit should be briefly summarised and discussed. The presentation should not simply repeat the description of results nor introduce new results.*

*The discussion and conclusions should clearly identify any new or unexpected findings, comment on their significance and discuss any potential problems such as inconsistencies between related measures. The clinical relevance and importance of the results should also be discussed in the light of other existing data.*

## 11. ACKNOWLEDGMENTS

## 12. REFERENCES

References should be numbered according to the order in which they are cited in the text of the report. The following style should be applied:

1. Harris NL, Jaffe ES, Stein EH et al. A Revised European-American Classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-2.

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## 13. TABLES AND FIGURES REFERRED TO IN THE TEXT

*All tables and figures from which data mentioned/presented in Sections 7-10 of the report are derived, should be placed in this section and cross-referenced.*

## 14. LIST OF APPENDICES

### 14.1 STUDY INFORMATION

- 14.1.1 Protocol and protocol amendments
- 14.1.2 Sample case report form (unique pages only)
- 14.1.3 List and description of investigators
- 14.1.4 Signatures of sponsor's representative and Study Chair
- 14.1.5 Audit certificates (if available)
- 14.1.6 Publications based on the study (if available)

### 14.2. PATIENT DATA LISTINGS

- 14.2.1 Major protocol deviations
- 14.2.2 Patients excluded from the efficacy analysis (if applicable)
- 14.2.3 Deaths related to the study treatment(s) (if applicable)