

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

## ***PROTOCOL TEMPLATE - PHASE II, III or IV Trial***

*The protocol template is a tool to facilitate rapid protocol development. Any sections that do not apply to a specific study should contain the statement "not applicable". New section can be added if appropriate as sub-headings of the predefined sections. All protocol template instructions and prompts are in blue and italics. As you complete the information requested please delete the italicized text.*

### ***<Title>***

*The title should describe essential aspects of the study. Check that the following topics are inserted:*

*Phase, Design (e.g. dose finding), Randomized/not randomized, Level of blindness (single /double/ open), Adaptive (study in which changes can be done according to the preliminary results of the ongoing study, Name of drugs, single agent or combination, route of administration (e.g. oral, IV), Schedule (weekly, q28, q2wk), Subject population (e.g. adults, male and/or female, resistant/sensible, previously treated or not, target expression), Indication (e.g. solid tumors, lymphomas or specific disease as ovarian/breast/colon ca ...), Critical endpoints (e.g efficacy).*

IMP Identifiers: *Enter the IMP name/Code*

Protocol Number: *(Assigned by the sponsor)*

EudraCT Number: *(Applicable in EU countries)*

Protocol Version (Date): *V x.xx; (dd/mm/yyyy)*

*In case of amendment(s) list here the different protocol versions with relative dates*

Protocol including the amendment: *1P or 2P or 3P (dd/mm/yyyy)*

Sponsor: *Enter Name*

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*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## SPONSOR SIGNATURE

\_\_\_\_\_  
Sponsor Representative (printed name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## *STUDY CHAIR SIGNATURE (where applicable )*

\_\_\_\_\_  
Study Chair (printed name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

*DRUG NAME/CODE*

*Protocol Number*

*Protocol Version and Date*

## PRINCIPAL INVESTIGATOR AGREEMENT

I have read the Protocol entitled “<*Study title*>” and I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements. I will provide all study personnel under my supervision with all information provided by the Sponsor and I will inform them about their responsibilities and obligations.

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Principal Investigator (*of each site*)

(printed name, Institution, Department and location)

---

Signature

---

Date

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## ADDITIONAL TRIAL PERSONNEL/SITE INFORMATION

<b>Sponsor</b>	Name: Address: Phone: Fax:
<b>Sponsor authorized representative</b>	Name/title: Address: Phone: Fax: E-mail:
<b>Study Chair</b>	Name/title: Address: Phone: Fax: E-mail:
<b>Principal Investigator (of each site)</b>	Name/title: Address: Phone: Fax: E-mail:
<b>Safety desk (SAE Reporting)</b>	Name: Address: Phone: Fax: E-mail:
<b>Central laboratory for .....</b>	Name of laboratory: Name of reference person: Address: Phone: Fax: E-mail:

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## TABLE OF CONTENTS

<b>1</b>	<b>SYNOPSIS.....</b>	<b>7</b>
<b>2</b>	<b>STUDY FLOW CHART .....</b>	<b>9</b>
<b>3</b>	<b>SCHEDULE OF EVENTS .....</b>	<b>10</b>
<b>4</b>	<b>ABBREVIATIONS AND DEFINITIONS OF TERMS .....</b>	<b>11</b>
<b>5</b>	<b>BACKGROUND INFORMATION .....</b>	<b>13</b>
<b>6</b>	<b>STUDY RATIONALE.....</b>	<b>13</b>
<b>7</b>	<b>STUDY OBJECTIVES.....</b>	<b>13</b>
7.1	PRIMARY OBJECTIVE .....	13
7.2	SECONDARY OBJECTIVE(S).....	13
<b>8</b>	<b>STUDY ENDPOINTS .....</b>	<b>13</b>
8.1	PRIMARY ENDPOINT .....	13
8.2	SECONDARY ENDPOINT(S).....	13
<b>9</b>	<b>STUDY DESIGN .....</b>	<b>14</b>
<b>10</b>	<b>STUDY POPULATION .....</b>	<b>14</b>
10.1	SUBJECT SELECTION .....	14
10.1.1	Subject Inclusion Criteria .....	14
10.1.2	Subject Exclusion Criteria .....	14
10.2	SCREENING FAILURES .....	14
10.3	REPLACEMENTS .....	14
<b>11</b>	<b>ENROLLMENT PROCEDURES .....</b>	<b>14</b>
<b>12</b>	<b>STUDY TREATMENT .....</b>	<b>14</b>
12.1	TRIAL PRODUCT (S) .....	14
12.2	DRUG PREPARATION (IF NOT INCLUDED IN A SPECIFIC MANUAL) .....	15
12.3	TREATMENT DOSE AND SCHEDULE .....	15
12.4	DURATION OF TREATMENT .....	15
12.5	DRUG ACCOUNTABILITY .....	15
12.6	TREATMENT DOSE MODIFICATIONS .....	15
12.7	CONCOMITANT MEDICATIONS AND OTHER THERAPY .....	15
<b>13</b>	<b>SUBJECT WITHDRAWAL FROM STUDY PARTICIPATION .....</b>	<b>15</b>
<b>14</b>	<b>TREATMENT ASSESSMENT .....</b>	<b>16</b>
14.1	PRE-TREATMENT EVALUATIONS .....	16
14.2	ON STUDY EVALUATIONS.....	16
14.3	OFF TREATMENT EVALUATIONS.....	16
14.4	FOLLOW-UP EVALUATIONS.....	16
14.5	DETAILS OF INDIVIDUAL ASSESSMENTS .....	16
14.6	OTHER STUDIES (IF APPLICABLE) .....	16
<b>15</b>	<b>SAFETY ASSESSMENTS .....</b>	<b>16</b>
15.1	PRE-EXISTING CONDITION.....	16
15.2	ADVERSE EVENT ASSESSMENT.....	16
15.3	ADVERSE EVENT REPORTING PERIOD .....	18
15.4	REPORTING PROCEDURES FOR ADVERSE EVENT .....	18

*DRUG NAME/CODE*

*Protocol Number*

*Protocol Version and Date*

15.5	RECORDING ADVERSE EVENTS IN THE CASE REPORT FORMS.....	19
15.6	CAUSALITY ASSESSMENT AND GRADING OF ADVERSE EVENT SEVERITY .....	20
15.7	EXPOSURE IN UTERO .....	21
15.8	OVERDOSE.....	21
15.9	FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS .....	21
<b>16</b>	<b>EFFICACY ASSESSMENTS .....</b>	<b>21</b>
16.1	DEFINITION OF EFFICACY PARAMETERS .....	21
<b>17</b>	<b>STATISTICAL METHODS .....</b>	<b>21</b>
17.1	SAMPLE SIZE CALCULATION .....	21
17.2	STUDY POPULATION .....	22
17.3	ANALYSIS .....	22
17.3.1	Study Conduct and Subject Disposition .....	22
1.1.1	Baseline Characteristics and treatment Group Comparability .....	22
1.1.2	Treatment Analysis .....	22
1.1.3	Safety Analysis .....	22
1.1.4	Other studies analysis, if applicable .....	23
1.1.5	Efficacy Analysis.....	23
<b>18</b>	<b>QUALITY CONTROL AND QUALITY ASSURANCE .....</b>	<b>23</b>
18.1	MONITORING .....	23
18.2	AUDITING .....	23
18.3	LABORATORY REQUIREMENTS .....	23
<b>19</b>	<b>DATA HANDLING AND RECORD KEEPING .....</b>	<b>24</b>
19.1	CASE REPORT FORM (CRF).....	24
19.2	DATA HANDLING .....	24
19.3	RECORD RETENTION .....	24
<b>20</b>	<b>ETHICAL CONSIDERATION .....</b>	<b>24</b>
20.1	INSTITUTIONAL REVIEW BOARD(IRB)/ INDEPENDENT ETHICS COMMITTEE (IEC) AND COMPETENT AUTHORITY (CA) .....	24
20.2	ETHICAL CONDUCT OF THE TRIAL .....	25
20.3	INFORMED CONSENT .....	25
<b>21.</b>	<b>STUDY DISCONTINUATION CRITERIA .....</b>	<b>25</b>
<b>22</b>	<b>LIABILITY AND INSURANCE .....</b>	<b>26</b>
<b>23</b>	<b>CONFIDENTIALITY OF INFORMATION AND PUBLICATION OF RESULTS .....</b>	<b>26</b>
<b>24</b>	<b>REFERENCES .....</b>	<b>26</b>
<b>25</b>	<b>APPENDICES .....</b>	<b>26</b>

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## 1 SYNOPSIS

Protocol Title:	<i>See note in cover page</i>	
Protocol Number:		
IMPs:	<ul style="list-style-type: none"> <li>• <i>Name/code first product</i></li> <li>• <i>Formulation</i></li> <li>• <i>Unit strength</i></li> <li>• <i>Supplier</i></li> </ul>	<ul style="list-style-type: none"> <li>• <i>Name/code second product( if applicable)</i></li> <li>• <i>Formulation</i></li> <li>• <i>Unit strength</i></li> <li>• <i>Supplier</i></li> </ul>
Participating countries		
List of study centres		
Background Information and Study Rationale	<p><i>The aim of this section is to very briefly define WHY the trial should be done. Critical topics are:</i></p> <ul style="list-style-type: none"> <li>- <i>medical need</i></li> <li>- <i>available current therapies and opportunities of the product/s on study (e.g. oral drugs versus IV, less toxicities, best efficacy, schedule that guarantees a best compliance, lower cost)</i></li> <li>- <i>summary of available clinical data.</i></li> <li>- <i>doses and schedule choice rationale, only if different from standard.</i></li> </ul> <p><i>Reference documentation to be used: IB, papers, other trials</i></p>	
Primary Objective	<p><i>The objectives are the questions to be answered (e.g. activity).</i></p> <p><i>Only <u>one</u> primary objective should be defined</i></p>	
Secondary Objective(s)	<p><i>More than one. E.g.</i></p> <ul style="list-style-type: none"> <li>• <i>Safety profile</i></li> <li>• <i>Survival, duration of response</i></li> </ul>	
Primary Endpoint	<p><i>The endpoints are the parameters to be measured to reach the objectives (e.g. response rate). Very important is to ensure the consistency between objectives and endpoints.</i></p>	
Secondary Endpoint(s)	<p><i>More than one. E.g.</i></p> <ul style="list-style-type: none"> <li>• <i>Description of the frequency and severity of Adverse Events based on the NCI –CTCAE V3.0</i></li> <li>• <i>TTP, PFS, OS</i></li> </ul>	
Study Design	<p><i>Provide briefly a justification to explain HOW the trial will be done. Describe the main methods applied to the conduct of the study:</i></p>	

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

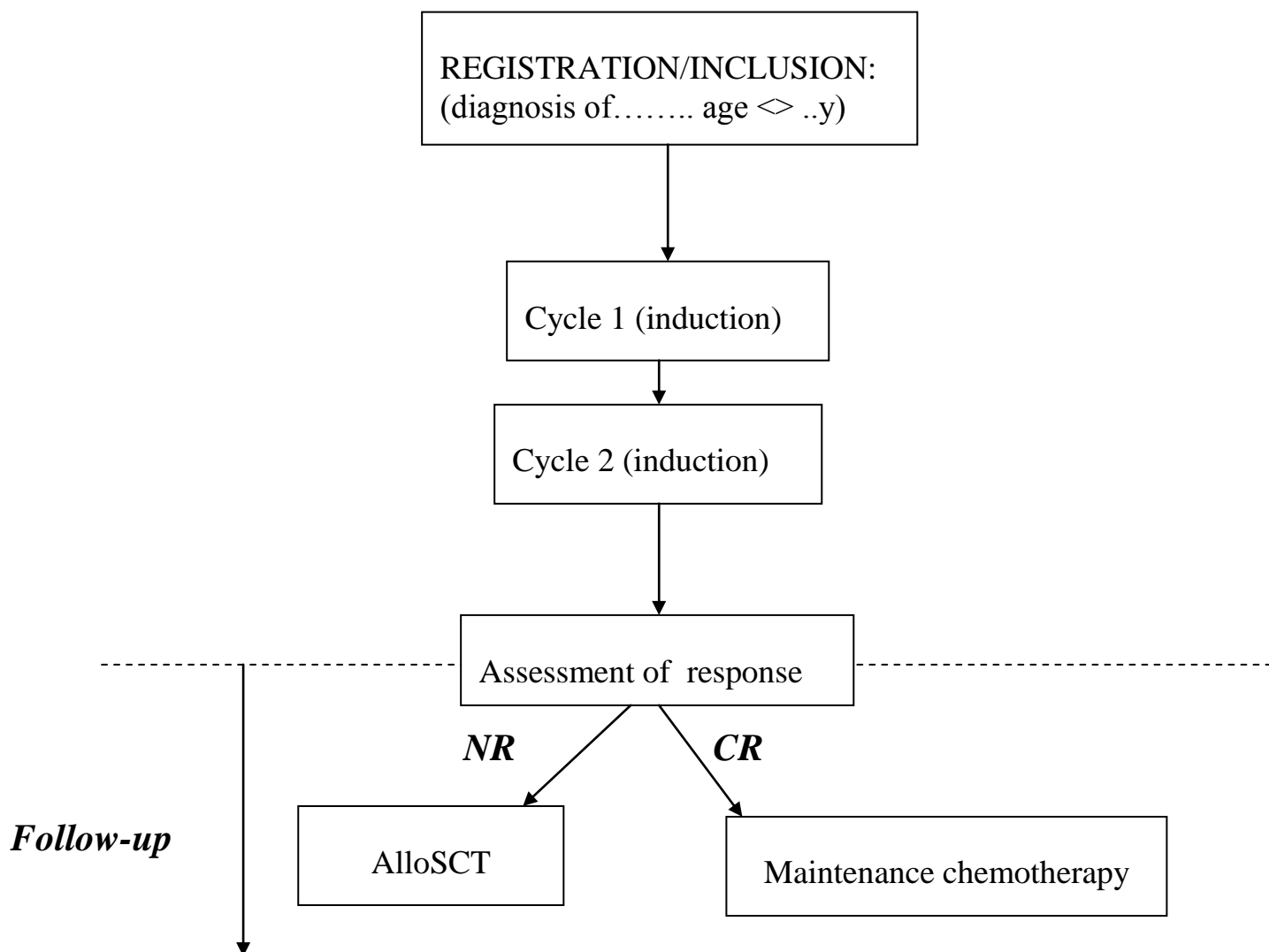
	<ul style="list-style-type: none"> <li><i>phase of study</i></li> <li><i>treatment group allocation (e.g. randomized)</i></li> <li><i>patients stratification ( if any)</i></li> <li><i>blinding level (open label)</i></li> <li><i>setting (e.g. multicentric)</i></li> <li><i>ancillary studies if any</i></li> <li><i>definition of study conclusion</i></li> </ul>
Treatment	<ul style="list-style-type: none"> <li><i>Dose, route and schedule of administration</i></li> <li><i>If combination of drugs, explain sequence of drugs (rational)</i></li> </ul>
Treatment Duration	<i>Specify the treatment duration and when a patient should be replaced</i>
Supportive Therapy	<i>E.g. prophylaxis or pre-treatment. Specify dose and schedule and condition if any</i>
Efficacy Assessments	
Safety Assessments	<i>CTCAE. If applicable describe if a special scale is required for specific toxicity (e.g. TNS scale for neurological toxicity)</i>
Other assessments	<i>When and how many and what material blood or urine or tissue; for blood specify maximum total volume per pt.</i>
Sample Size	<i>Indicate statistical method used, assumptions for efficacy and sample size derived from them</i>
Inclusion Criteria	<p>Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:</p> <ol style="list-style-type: none"> <li><i>Diagnosis</i></li> <li><i>Age (e.g. <math>\geq 18</math>, <math>\leq 75</math>, )</i></li> <li><i>Gender</i></li> <li><i>.....</i></li> <li><i>.....</i></li> </ol>
Exclusion criteria	<p>Subjects does not have to meet all the following esclusion criteria to be eligible for enrolment into the study:</p> <ol style="list-style-type: none"> <li><i>.....</i></li> <li><i>.....</i></li> <li><i>.....</i></li> <li><i>.....</i></li> <li><i>.....</i></li> </ol>
Patients replacement	<i>Describe criteria for replacing patient</i>
Planned study timelines	<p><i>Duration of enrolment:</i></p> <p><i>Expected FPI:</i></p> <p><i>Expected LPO:</i></p> <p><i>Expected LPLV:</i></p> <p><i>Duration of whole study (from FPI to LPLV):</i></p>



*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## 2 STUDY FLOW CHART

Example



*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

### 3 SCHEDULE OF EVENTS

Assessment /events	Screening (day)	Treatment (day)						EOT visit	F-up
		Cycle 1			Cycle 2				
	<i>-14 To 0</i>	<i>DI</i>	<i>Dx</i>	<i>Dy</i>	<i>DI</i>	<i>Dx</i>	<i>Dy</i>	<i>+14 To 28</i>	
Signed ICF									
Demographic data									
Medical History									
Baseline conditions									
Vital signs									
Physical examination									
PS (ECOG)									
Hematology									
Blood Chemistry									
Pregnancy test									
Urinalysis									
LVEF									
ECG									
Chest X-ray1									
Prior and Concomitant treatment									
PK sampling									
PD sampling									
DRUG X administration									
Adverse event monitoring									

Footnotes for Schedule of Events.

*Day 0: Within 24 hrs before treatment*

*Day 1: First day of administration*

*EOT: end of treatment visit to be performed 14 to 28 days following the last dose of study drug*

*Follow-up: specify timing*

*Tumor history: diagnosis and prior therapy (e.g. radiotherapy, systemic therapies)*

*Hematology: Hematocrit, Hemoglobin, Red blood count, White Blood Cell with differential count for neutrophils, lymphocytes, monocytes, basophils and eosinophils., platelets*

*Chemistry: electrolytes (sodium, potassium and magnesium, calcium, chloride and bicarbonate), Enzymes (ASAT/SGOT, ALAT/SGPT, ALP, GGT, troponina I, CPK, LDH), Biological Bioproduct test (Glucose, Creatinine Phosphorus, BUN, total bilirubin, Cholesterol, Triglycerides), total protein, albumin*

*Pregnancy test required for women of childbearing potential only. Specify if urine or blood*

*Urinalysis: deep stick or other*

*Adverse event monitoring: continuously during the study*

DRUG NAME/CODE  
Protocol Number  
Protocol Version and Date

#### 4 ABBREVIATIONS AND DEFINITIONS OF TERMS

*To be modified according to protocol wording*

<i>AE</i>	<i>adverse event</i>
<i>ALT</i>	<i>alanine aminotransferase</i>
<i>ANC</i>	<i>absolute neutrophil count</i>
<i>aPTT</i>	<i>activated partial thromboplastin time</i>
<i>AST</i>	<i>aspartate aminotransferase</i>
<i>AUC</i>	<i>area under the plasma drug concentration versus time curve</i>
<i>AUC<sub>0-X</sub></i>	<i>area under the plasma drug concentration versus time curve from time zero to X hours after study drug administration</i>
<i>AUC<sub>0-∞</sub></i>	<i>area under the plasma drug concentration versus time curve from time zero to infinity</i>
<i>BID</i>	<i>bis in die/ twice a day</i>
<i>BSA</i>	<i>body surface area</i>
<i>BWC</i>	<i>body weight change</i>
<i>BUN</i>	<i>blood urea nitrogen</i>
<i>CA</i>	<i>Competent Authority</i>
<i>CBC</i>	<i>complete blood count</i>
<i>CFR</i>	<i>Code of Federal Regulations</i>
<i>C<sub>max</sub></i>	<i>maximum observed plasma drug concentration</i>
<i>CR</i>	<i>complete response</i>
<i>CrCl/CL<sub>CR</sub></i>	<i>creatinine clearance</i>
<i>CRA</i>	<i>clinical research associated</i>
<i>CRF (eCRF)</i>	<i>case report form (electronic case report form)</i>
<i>CT</i>	<i>computerized tomography</i>
<i>CTCAE</i>	<i>Common terminology criteria for adverse events</i>
<i>CYP3A4</i>	<i>human cytochrome P450 3A4</i>
<i>EC</i>	<i>Ethics Committee</i>
<i>ECG</i>	<i>electrocardiography, electrocardiogram</i>
<i>ECOG</i>	<i>Eastern Cooperative Oncology Group</i>
<i>EE</i>	<i>Efficacy evaluable</i>
<i>EMA</i>	<i>European Medicines Agency</i>
<i>FDA</i>	<i>US Food and Drug Administration</i>
<i>GCP</i>	<i>Good clinical practices</i>
<i>GGT</i>	<i>gamma-glutamyl transpeptidase</i>
<i>Hb</i>	<i>hemoglobin</i>
<i>ICF</i>	<i>Informed consent form</i>

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

<i>ICH</i>	<i>International Conference on Harmonisation</i>
<i>IMP</i>	<i>Investigational Medicinal Product</i>
<i>IND</i>	<i>Investigational New Drug</i>
<i>INR</i>	<i>international normalized ratio</i>
<i>IRB</i>	<i>Institutional Review Board</i>
<i>IUD</i>	<i>intrauterine device</i>
<i>IV</i>	<i>intravenous</i>
<i>LDH</i>	<i>lactate dehydrogenase</i>
<i>MedDRA</i>	<i>Medical Dictionary for Regulatory Activities</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>MTD</i>	<i>maximum tolerated dose (or dosage)</i>
<i>MWT</i>	<i>Maintenance of Wakefulness Test</i>
<i>NHL</i>	<i>Non-Hodgkins 's Lymphomas</i>
<i>NOAEL</i>	<i>No observed adverse effect level</i>
<i>PD</i>	<i>Progressive disease</i>
<i>PI</i>	<i>Principal investigator</i>
<i>PWB</i>	<i>Peripheral Whole Blood</i>
<i>PLTs</i>	<i>Platelets /thrombocytes</i>
<i>p.o.</i>	<i>Per os/oral</i>
<i>PR</i>	<i>Partial response</i>
<i>PS</i>	<i>Performance status</i>
<i>PT</i>	<i>prothrombin time</i>
<i>Q</i>	<i>Quaque / every</i>
<i>QA</i>	<i>Quality assurance</i>
<i>QD</i>	<i>Quaque die / every day</i>
<i>RBC</i>	<i>red blood cell</i>
<i>RD</i>	<i>Recommended Dose</i>
<i>RECIST</i>	<i>Response evaluation criteria in solid tumors</i>
<i>SAE</i>	<i>Serious adverse event</i>
<i>sc</i>	<i>subcutaneous</i>
<i>SD</i>	<i>Stable disease</i>
<i>SDV</i>	<i>source document verification</i>
<i>SE</i>	<i>Safety evaluable</i>
<i>SOP</i>	<i>standard operating procedure</i>
<i>t<sub>1/2</sub></i>	<i>elimination half-life</i>
<i>t<sub>max</sub></i>	<i>time to maximum observed drug concentration</i>
<i>ULN</i>	<i>upper limit of the normal range</i>

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

$V_{ss}$	<i>volume of distribution at steady state</i>
$V_z$	<i>volume of distribution</i>
VEGF	<i>Vascular endothelial growth factor</i>
WBC	<i>white blood count / white blood cells</i>
WHO	<i>World Health Organization</i>
WHO DD	<i>World Health Organization (WHO) drug dictionary</i>
WOCBP	<i>Woman of child bearing potential</i>

## 5 BACKGROUND INFORMATION

- *Description of medical condition/need*
- *Information on current therapies for the medical condition (including the shortcoming, if any)*
- *Description of the investigational drug as related to medical condition*
- *Name, pharmacological class and description of the investigational drug, mechanism of action*
- *Summary of findings from clinical trials that are relevant to the study*
- *Summary of clinical safety*

## 6 STUDY RATIONALE

- *Evaluation of potential risks and benefits ratio*
- *Description of reason to investigate the IMP or the combination of the IMP(s)*
- *Description of and justification for the route of administration, dosage, dosage regimens and the treatment period(s)*

## 7 STUDY OBJECTIVES

### 7.1 Primary Objective

- *From synopsis*

### 7.2 Secondary Objective(s)

- *From synopsis*

## 8 STUDY ENDPOINTS

### 8.1 Primary Endpoint

- *From synopsis*

### 8.2 Secondary Endpoint(s)

- *From synopsis*

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

## 9 STUDY DESIGN

*This section should provide a description of trial and how it will be done. The following topics should be included:*

- *phase of study*
- *treatment group allocation (e.g. randomized)*
- *blinding level (open label)*
- *setting (e.g. multicentric)*
- *IMP administration dose and schedule*
- *duration of treatment*
- *ancillary studies if any*
- *statistical methods (if a two step design is chosen describe rules for entering second step)*
- *definition of study conclusion.*

## 10 STUDY POPULATION

### 10.1 Subject Selection

#### 10.1.1 Subject Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for enrolment into the study:

*Insert criteria from synopsis*

#### 10.1.2 Subject Exclusion Criteria

The presence of any following will exclude a subject from study enrolment:

*Insert criteria from synopsis*

### 10.2 Screening failures

For all screened patients, a “Subject Screening Log” will be completed and in case of screening failure the reason(s) for failure will be documented. CRFs have to be completed only for registered patients.

### 10.3 Replacements

Patients not evaluable for efficacy according to the definition described in section **XXXX** will be replaced.

## 11 ENROLLMENT PROCEDURES

Before any screening procedure all patients must sign a written informed consent for the study. The following logs must be maintained at each study site and kept in the Investigator File: a “Subject Screening Log”, to document the identification of subjects who enter screening, a “Subject Identification Code List” for all subjects registered to maintain the correlation with the patient's full identification data (name, surname - confidential), and a “Subject Enrolment Log”, to document chronological enrolment of patients. Upon review of all inclusion/exclusion criteria, if the patient is eligible, a progressive “Registration Number”, is centrally assigned by **XXXX**....

Any controversial eligibility assessment will be discussed with the **YYY** and **ZZZ**.

## 12 STUDY TREATMENT

### 12.1 Trial Product (s)

*Name, Formulation, Unit Strength, Supplier, Storage, Stability, Procedure for Handling (for all investigational drugs)*

DRUG NAME/CODE  
Protocol Number  
Protocol Version and Date

## 12.2 Drug preparation (if not included in a specific manual)

XXXXXX

## 12.3 Treatment Dose and Schedule

Study drug(s) will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

XXXXXX

## 12.4 Duration of Treatment

*Specify min treatment, max treatment (if applicable), reasons requiring treatment withdrawal.*

## 12.5 Drug Accountability

The Investigator and/or a pharmacist or other appropriate individual designated by the Investigator, should maintain records of the amount of investigational drug delivered to the trial site, the inventory at the site, the amount of drug administered to each subject and *the unused drug to be returned to the Drug Company or to be destroyed locally.*

The pharmacist, or a delegated person at the site, will be responsible for handling study drug(s) preparation of the appropriate doses to be administered, and completion of drug accountability forms.

Study drug(s) must be handled and administered strictly in accordance with the protocol and/or the specific manual and will be stored in a limited access area or in a locked cabinet under appropriate storage conditions. Study drug(s) should be administered under the supervision of the investigator or co-investigator, only to subjects participating in the study in accordance with the approved protocol.

Unused study drug(s) must be available for verification by the sponsor's site monitor during on site monitoring visits.

*In case of oral treatment consider the possibility to use a patient diary to monitor treatment compliance.*

*In case commercial drug is used in the trial, the same procedure of study drug must be followed and if it possible a drug accountability must be maintained as the study drug.*

## 12.6 Treatment Dose Modifications

*Describe the expected toxicities (haematological and non haematological) which require dose modifications and/or dosing delays in subsequent cycles, using tables.*

## 12.7 Concomitant Medications and Other Therapy

- Supportive therapies (specify dose and schedule and condition if any)
- Required (or allowed) concurrent therapies
- Prohibited concurrent therapies

## 13 SUBJECT WITHDRAWAL FROM STUDY PARTICIPATION

In accordance with the current revision of the Declaration of Helsinki and other applicable regulations, a subject (or a legally acceptable representative) has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

The patient has to be discontinued from the study for the following reasons:

- *Progressive disease at any time*
- *Occurrence of an unacceptable toxicity*



DRUG NAME/CODE

Protocol Number

Protocol Version and Date

- *General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator*
- *Pregnancy*
- *Other reasons to be added as appropriate*

At the time of withdrawal, the investigator should schedule the End of Treatment and Follow-up visits in agreement with the patient.

## 14 TREATMENT ASSESSMENT

### 14.1 Pre-Treatment Evaluations

*Specify type and, time of assessments as reported on the "Schedule of events"*

### 14.2 On Study Evaluations

*Specify type and, time of assessments as reported on the "Schedule of events"*

### 14.3 Off Treatment Evaluations

*Specify type, time of assessments as reported on the "Schedule of events"*

### 14.4 Follow-Up Evaluations

*Specify type, time of assessments as reported on the "Schedule of events"*

### 14.5 Details of Individual Assessments

- *Instrumental assessments*
- *Laboratory assessments*
- *Clinical assessments*

### 14.6 Other Studies (If applicable)

*XXXXX....*

## 15 SAFETY ASSESSMENTS

The toxicities will be evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTCAE) .....

### 15.1 Pre-existing condition

All active/symptomatic conditions present in the *last 7 days before* study treatment start are to be collected in the same format as AEs and represent the reference picture for the identification of treatment emergent AEs (see definition below).

Any new condition and any worsening of pre-existing condition occurring after Informed Consent signature and before study treatment start are to be considered for Serious Adverse Event (SAE) reporting (see 14.2).

### 15.2 Adverse Event Assessment

Adverse Events (AE)

An adverse event is any untoward medical occurrence in a patient that is administered a drug or biologic (medical product); the event does not necessarily have a causal relationship with that treatment or usage. Adverse events include the following:



*DRUG NAME/CODE*

*Protocol Number*

*Protocol Version and Date*

- All suspected medication adverse reactions
- All reaction from medication overdose, abuse, withdrawal, sensitivity, or toxicity
- Apparently unrelated illness, including the worsening of a pre-existing illness
- Injury or accidents. Note that if a medical condition is known to have caused an injury or accident (e.g., a fracture due to a fall secondary to dizziness), the medical condition (dizziness) and the injury (fracture) should be reported as 2 separate adverse events.
- Laboratory abnormalities and abnormalities in physiological testing or physical examination findings that require clinical intervention (e.g. therapeutic measures, IMP dose and/or schedule changes) or further investigation (beyond ordering a repeat [confirmatory] test) or that are considered clinically significant by the investigator

#### Any events

Each adverse event is to be classified by the investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed. Progression of disease intended as increase of tumour burden should not be reported as an adverse event, while any clinical sign/symptom/illness associated with malignant disease progression should be recorded as adverse event.

*Specify, if appropriate, any other events excluding from AE reporting*

#### Serious Adverse Events (SAE)

The definition of seriousness is based on the patient/event outcome or action criteria associated with events that pose a threat to patient's life or functioning.

An adverse event that meets one or more of the following definition is classified as serious:

- Results in death
- Is life-threatening (i.e., the patient was at risk of death at the time of the event; it is not referred to cases in which the event might have caused death if it was more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based on the investigator's medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered serious include hospitalizations which are:

- a) elective and planned before entry into the study
- b) emergency and do not result in overnight hospitalization, unless fulfilling the criteria above
- c) for the routine treatment of study indication and not associated with any deterioration in condition.

In all other cases, the hospitalization seriousness criterion is met as long as hospitalization is required which does not necessarily correspond to the actual hospitalization period (e.g., a patient might be admitted to hospital two days after this measure was required because the investigator was not informed of the patient's conditions)

*List any specific AEs that must be considered serious by default regardless if they meet the seriousness criteria*

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

*List any specific AE that are not to be reported and processed as SAEs even though they meet the seriousness definition (e.g. expected events associated with disease progression).*

### 15.3 Adverse Event Reporting Period

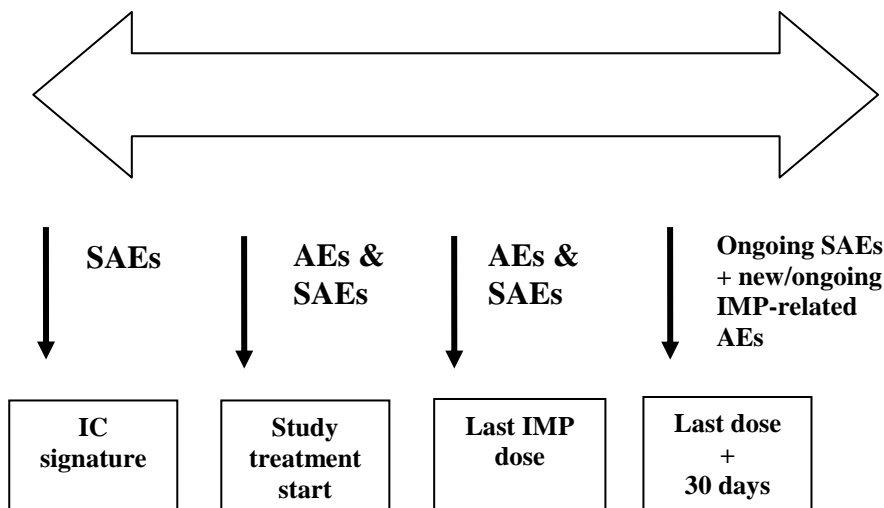
During the screening period - from informed consent signature until first IMP administration – the occurrence of any SAEs will be reported following the SAE reporting procedure described in Section 14.3.

Apart from SAEs, for which the reporting period starts earlier, the adverse event reporting period begins upon receiving the first IMP dose and ends *30 days after the last IMP dose*.

*The AE reporting period following the last IMP dose should be sufficiently long to capture any delayed toxicities and should be determined on the basis of the IMP half-life.*

All adverse events that occur in trial patients during the adverse event reporting period specified above must be reported to **YYYYY** whether or not the event is considered medication related. In addition, any untoward event that occurs subsequent to the adverse event reporting period that the investigator becomes aware of and assesses as at least possibly related to the study treatment should also be reported as an adverse event.

AEs assessed by the investigators as unrelated to the IMP(s) must be followed until resolution or *until 30 days after the last IMP dose* whichever occurs earlier. AEs assessed by the Investigator as related to the IMP and SAEs of any causality must be followed until resolution or death if this occurs beyond the AE reporting period defined above, unless the patient is lost to follow-up or start a new systemic anti-tumor therapy or the event has stabilized and is assessed as chronic by the Investigator.



### 15.4 Reporting procedures for Adverse Event

Each adverse event is to be classified by the investigator as **SERIOUS** or **NON-SERIOUS**. This classification of the gravity of the event determines the reporting procedures to be followed. If a serious adverse event occurs, the **YYYYY (fax + 39 .....)** is to be notified, using the SAE report form, within 24 hours of awareness of the event by the investigator. If the initial report is incomplete or the event is still ongoing at the time of reporting or if new significant information becomes available, this report is to be followed by submission of follow-up information within 5 calendar days after the initial notification. Reporting requirements for adverse events are summarized in the following table.

DRUG NAME/CODE  
Protocol Number  
Protocol Version and Date

## REPORTING REQUIREMENTS FOR ADVERSE EVENT

Gravity	Reporting Time	Type of Report
SERIOUS	Within 24 hours from awareness by the investigator	Initial report on SAE report form + case report form
	Within 5 calendar days from initial report	Follow-up/Final report on SAE report form
NON SERIOUS	Per case report form submission procedure	Case report form

If for any reason the SAE form transmission is not possible, **YYYYY** should be informed by phone (+39....) of the occurrence of the event. In this exceptional case, **YYYYY** will complete a SAE form with information received, which will be sent to the investigator for confirmation, and in the meanwhile pharmacovigilance procedures will be initiated.

**YYYYY** will submit to the concerned drug Company(ies) all SAEs occurring in this trial, regardless of whether the investigator suspects causality with the study treatment.

Serious adverse events should also be reported on the adverse event case report form. The form to be used for serious adverse event expedited reporting is not the same as the adverse event case report form, but where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

**YYYYY** is responsible to assess each SAE reported by the study Investigators to identify any suspected unexpected serious adverse reactions (SUSAR), i.e. serious adverse events considered at least possible associated to the study treatment by either the Investigator or **YYYYY** and not listed in the IMP(s) reference document(s)

*Specify if IB or SPC for each IMP). In case of IMP combination specify if causality assessment is to be provided separately for each IMP or for the study treatment overall.*

If a SAE is assessed as a possible SUSAR **YYYYY** may urgently require further information from the Investigator. **YYYYY** will issue a SUSAR (Suspect Unexpected Serious Adverse Reaction) notification whenever appropriate and submit it to all investigators involved in any study sponsored by **YYYYY** using the suspected IMP(s) as well as to Eudravigilance, the concerned Ethics Committees and Competent Authorities.

Follow-up information is to be reported on a new serious adverse event form and transmitted to the same fax number as the initial report. A follow-up report is to be filled in, not only to complete the information provided on the initial report but also to modify any incorrect data.

The SAE fax delivery confirmation sheets must be retained at the study sites.

At the end of the study all original SAE report forms are to be collected by CRA and delivered to **YYYYY** for archiving in the TMF, while the corresponding copies must be retained in the ISF.

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

AEs can be assessed directly by the Investigator during a clinical visit or based on laboratory/Instrumental examinations or can be referred by the patient.

*Specify if a patient diary is to be used for AEs collection and how the recorded information is to be handled (a patient diary can be considered as source document and therefore all AEs reported by patients should be inserted in the CRF or it can just give indication to the Investigator, but AEs should be verified by the investigator before being reported in the DB)*

DRUG NAME/CODE  
Protocol Number  
Protocol Version and Date

*AEs should be reported whenever possible in terms of diagnosis rather than signs and symptoms.*

- Pre-existing Conditions

A pre-existing condition (i.e., a disorder starting before the adverse event reporting period) should not be reported as an adverse event unless the condition worsens during the adverse event reporting period.

- Procedures

Diagnostic and therapeutic procedures, such as surgery, should not be reported as adverse events, while the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an appendectomy performed for an acute appendicitis occurring during the adverse event reporting period should not be reported as adverse event; while “acute appendicitis” is to be reported as adverse event. If a patient undergoes a surgical procedure that was planned prior to entry into the trial, and surgery is not performed due to a worsening of a baseline condition, this baseline condition should not be reported as an adverse event.

- Symptoms of Targeted Disease

Tumour-related signs and symptoms will be followed at each visit. Although a measure of efficacy, these will always be reported as pre-existing conditions at baseline and during treatment only if they meet the definition of adverse event.

For all adverse events the Investigator will be asked to assess its relationship with each IMP or with the study treatment (*depending if causality assessment is to be provided separately for each IMP or for the study treatment overall*).

## 15.6 Causality assessment and Grading of Adverse Event Severity

The assessment of relationship to study drug and relevant WHO definitions will be done according to the following causality scale:

- ✓ Certain: 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
- ✓ Probable: 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 fulfil this definition.
- ✓ Possible: A clinical event, 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
- ✓ Unlikely: A clinical event, 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

Severity grading of adverse events and pre-existing conditions will be done according to the National Cancer Institute (NCI) Common Toxicity Criteria (*CTCAE*) Vxxx or updated versions.

Note the distinction between the gravity and the intensity of an adverse event. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity but would not be classified as serious unless it meets one of the criteria for serious events listed above.

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## 15.7 Exposure in Utero

If any trial patient becomes or is found to be pregnant while receiving the study drug or within 90 days of last IMP dose, the investigator submits this information following the same procedure as for SAEs. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induce termination of pregnancy).

The investigator will follow the patient until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify the **YYYYY SAFETY DESK** of the outcome within 5 days or as specified below. The investigator will provide this information as a follow up to the initial exposure in utero notification. The reason(s) for an induced abortion must be specified.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow procedures for reporting serious adverse events, i.e., report the event to **YYYYY**.

Additional specification of pregnancy outcomes that are classified as serious adverse events:

- “Spontaneous abortion” includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should also be reported

## 15.8 Overdose

Reporting if any of overdose (accidental or intentional) which results in serious adverse reactions is to be handled following the SAE procedures. This includes reports related to drug intake with suicidal intentions and consequent drug overdose.

Overdose reporting even not associated with adverse reactions shall be anyhow reported immediately to **YYYYY**, using the most rapid type of communication (phone, e-mail).

## 15.9 Follow-up of Unresolved Adverse Events

All adverse events should be followed at least until 30 days following the last dose of IMP. Drug-related and serious adverse events ongoing at the end of this observation period must be recorded until they are resolved or the investigator assesses them as chronic or the subject is lost to follow-up or starts a new anti-cancer treatment, whichever occurs earlier.

## 16 EFFICACY ASSESSMENTS

### 16.1 Definition of efficacy parameters

**XXXXXXX** .....

## 17 STATISTICAL METHODS

### 17.1 Sample size calculation

*Indicate statistical method used (Simon's, other), assumptions for efficacy and sample size derived from them e.g.:*

*The study will accrue XX patients, XX during the stage 1 and XX during stage 2 according to Simon's two stage optimal design. The justification is the following:*



DRUG NAME/CODE

Protocol Number

Protocol Version and Date

*Expecting an overall XX% response rate, the drug will be considered insufficiently active if the RR is  $\leq X\%$  and very promising if the RR is  $\geq XX\%$ , for an XX% power.*

*If  $> X/XX$  patients enrolled in the first stage respond, the study will continue until a total of XX eligible and evaluable patients are treated.*

## 17.2 Study Population

Three populations will be considered for the analysis, as follows:

- The Safety Evaluable (SE) population defined as all treated patients (i.e. eligible as decided at the time of registration that receives at least 1 dose of study treatment). An incorrect treatment schedule or drug administration or an early termination of treatment does not result in exclusion of patients from this population. Patients with major deviations from the eligibility criteria affecting safety or from the treatment schedule at cycle 1 for reasons other than toxicity may be presented in separate tables/listings.
- The Intention to Treat (ITT) population defined as the SE population (i.e. eligible as decided at the time of registration that receives at least 1 dose of study treatment). An incorrect treatment schedule or drug administration or an early termination of treatment does not result in exclusion of patients from this population. Patients with major deviations from the eligibility criteria affecting safety or from the treatment schedule at cycle 1 for reasons other than toxicity may be presented in separate tables/listings.
- The Efficacy Evaluable (EE) population defined as all treated patients, with no major deviations from the eligibility criteria affecting efficacy evaluation, for whom the tumor response could be evaluated at least once while on treatment. These patients should have received at least 2 cycles after treatment starts, unless disease progression occurs at cycle 1.

## 17.3 Analysis

All patients who receive at least one dose *of either drug or of the combination (specify)* will be included in summary statistics, except for the analysis of study conduct and subject disposition for which all patients enrolled in the study will be displayed, even if not treated. Information will be provided concerning patient demographics, including baseline performance status, age and prior treatments.

### 17.3.1 Study Conduct and Subject Disposition

Patients satisfying the definition of the study populations will be tabulated and listed. The number of patients withdrawing from the study, not meeting the eligibility criteria, and who are considered protocol violators will also be described. Reasons why patients are excluded from any study population will be listed.

### 17.3.2 Baseline Characteristics and treatment Group Comparability

Patient characteristics at study entry will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables.

### 17.3.3 Treatment Analysis

The number of cycles administered, actual and total doses administered, absolute and relative dose intensity, dose modifications, delays and omissions, as well as reasons for deviation from planned therapy and overall duration of treatment will be described.

### 17.3.4 Safety Analysis

Safety and tolerability analysis will be applied on the SE population.

Adverse events physical examination, vital signs, concomitant medication, laboratory and instrumental data will be considered for the safety analyses. Descriptive statistics will be provided for these variables.

Adverse events will be coded using MedDRA dictionary at the lowest level term and their severity graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version x.x. Descriptive

*DRUG NAME/CODE*

*Protocol Number*

*Protocol Version and Date*

statistics will be provided by System Organ Class (SOC) and Preferred Term (PT). The analysis will focus on the events reported after the start of treatment (treatment emergent adverse events); the incidence of adverse event by treatment period (i.e. cycle1 and whole study period) will be calculated on a patient basis (i.e. counting the number of patients) and on a cycle basis (i.e. counting the number of cycles). In this analysis, patients/cycles will be classified according to the worst severity grade experienced during the analyzed time-window. Drug related adverse events will be evaluated in the same way.

Specific subsets of AEs, such as serious AEs, AEs leading to treatment discontinuation, AEs leading to treatment modification/schedule change will be identified in patients data listings

Haematological and biochemical toxicity will be graded according to the NCI CTCAE v3.0, and will be described by means of shift tables, reporting the worst grade observed during the analyzed time-window (cycle1, all cycles) vs. baseline grade.

Nadir/Zenith values, time to nadir/zenith and time to recovery may be explored for selected haematological/biochemical variables (specify the tests). Summary statistics will be presented by study period (cycle1, cycles > 1, all cycles).

Previous and concomitant medication will be tabulated while other relevant safety data will be reported in listings.

### **17.3.5 Other studies analysis, if applicable**

XXXXX

### **17.3.6 Efficacy Analysis**

XXXXXX

## **18 QUALITY CONTROL AND QUALITY ASSURANCE**

### **18.1 Monitoring**

Monitoring visits to the trial site will be made periodically during the trial by a qualified monitor to verify that the trial is conducted according to study protocol, GCP principles and regulatory requirements. The monitor will verify the accurate and complete recording of data on CRFs, source documents, Investigators File and drug accountability records.

The investigator/institution guarantees direct access to source documents of the study patients and to any other trial related documentation.

It is important that the investigator(s) and/or their relevant personnel are available during the monitoring visits.

### **18.2 Auditing**

Members of *Sponsor/YYYYY* may conduct an audit at site. The investigator will be informed if an audit is to take place and advised as to the scope of the audit.

Representative of regulatory agency may also conduct an inspection of the study. If informed of such an inspection, the Investigator should notify *Sponsor/YYYYY* immediately. The investigator will ensure that the auditors/ inspectors have access to the clinical supply, study site facilities, source documents and all study files.

### **18.3 Laboratory Requirements**

For laboratories handling clinical laboratory samples, the accreditation certificate and laboratory normal units and ranges must be provided to *YYYYY* and must be updated as needed by each study centre.

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## 19 DATA HANDLING AND RECORD KEEPING

### 19.1 Case Report Form (CRF)

An electronic Case Report Form will be completed for each enrolled subject. The language used must be English. The completed original Case Report Forms are the sole property of *Sponsor/YYYYY* and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities, without written permission from *Sponsor/YYYYY*.

The Investigator or an authorized staff member (medically qualified) has the responsibility to ensure completion and to review and sign all Case Report Forms.

However, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the Case Report Form.

Subject source documents are the hospital subject records maintained at the study site. In case where the source documents are the hospital chart, the information collected on the Case report Form must match with those charts. In some cases a portion of the source documents are not the hospital subject records. The investigator and *Sponsor/YYYYY* must agree which items will be recorded in the source documents and for which items the Case Report Form will stand as the source document. This must be stated in the "Data Location List" (filed in the Investigator File). One copy of this document should be remitted to YYYYYY for filing into the Trial Master File.

### 19.2 Data Handling

Data Management will be carried out by YYYYYY, Milan. Medical terms are coded according to the MedDRA dictionary. Data will be analyzed using SAS® System currently used at YYYYYY. Data cleaning will include both visual and computer-driven procedures in order to minimize logical inconsistencies and errors within the collected data. The data are checked for completeness, accuracy and consistency. The errors detected will be rectified by means of Data Clarification List (DCL) that will be used by the monitor for resolution of queries. The original DCF/DCL must be kept together with the patient CRF.

### 19.3 Record Retention

To enable evaluation and/or audits and/or regulatory authorities inspections, the Investigator agrees to keep records, including the identity of all participating subjects ("Subject identification code list"), all original signed informed consent forms, copies of all case report forms, source documents, detailed records of treatment disposition as well as the documentation included in the Investigator Trial File according to local regulations or as specified in the Clinical Trial Agreement.

If the Investigator relocates, retires, or for any reason withdraws from the study, *Sponsor/YYYYY* should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to YYYYYY. The investigator must obtain *Sponsor/YYYYY*'s written permission before disposing of any records.

## 20 ETHICAL CONSIDERATION

### 20.1 Institutional Review Board(IRB)/ Independent Ethics Committee (IEC) and Competent Authority (CA)

Before initiating the trial, the Investigator or *Sponsor/YYYYY* should have written favourable opinion from the IRB/IEC and CA for the trial conduction. All the correspondence with the IRB/IEC and CA should be retained in the Investigator File.

Before implementing any protocol amendment, the IRB/IRC/CA written approval must be obtained. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the IRB/IEC/CA must be notified in writing asap.



*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

It is responsibility of *Sponsor/YYYYY* to provide the Investigator with the Health Authority approval where needed to implement a trial.

## 20.2 Ethical conduct of the trial

The trial will be performed in accordance with International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki and applicable local regulatory requirements and laws.

## 20.3 Informed Consent

It is the responsibility of the investigator to give each patient (or the patient acceptable representative) full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patient must be informed about his/her right to withdraw from trial at any time. The patient should have time and opportunity to enquire about details of the trial and to decide whether or not to participate in the trial.

Written subject information must be approved by IRB/IEC and CA and must be given to each patient before any trial-related procedure is undertaken.

It is responsibility of the investigator to obtain informed consent signed and dated by the patient and by the medical person conducting the informed consent discussion, prior to undertaken any trial-related procedure. One copy of the signed and dated Informed Consent Form should be given to the patient. The originally signed document should be archived in the confidential section of the Investigator File.

The approved patient information sheet must not be changed without prior approval by *Sponsor/YYYYY* and by the IRB/IEC and CA.

When new study information arise during the study, the patients still on treatment must be informed and a new Informed Consent form or an addendum to the already signed Informed Consent form must be signed and dated by the patients.

If a patient becomes incompetent during the course of a trial where it was not anticipated, legally acceptable representative authorization should be obtained for a subject's continued participation.

## 21. STUDY DISCONTINUATION CRITERIA

This study may be prematurely terminated or suspended, if in the opinion of *Sponsor/YYYYY* there is sufficient reasonable cause. Written notification documenting the reason for study termination will be promptly provided to the investigator. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the study drug

After such a decision, the investigator must promptly contact all participating patients to inform them about the decision taken.

Should the study be closed prematurely or suspended the IRB/IEC and CA should also be informed promptly and provided with the reason for termination or suspension.

In case of termination the study materials must be collected and returned to the Sponsor and all Case Report Forms must be completed to the greatest extent possible.

*DRUG NAME/CODE*  
*Protocol Number*  
*Protocol Version and Date*

## 22 LIABILITY AND INSURANCE

The involved parties will be insured in accordance with the applicable laws and regulation for injuries and/or damages that may arise as a consequence of this trial.

## 23 CONFIDENTIALITY OF INFORMATION AND PUBLICATION OF RESULTS

All information regarding study drug supplied by *Sponsor/YYYYY* to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from *Sponsor/YYYYY*.

It is understood that there is an obligation to provide YYYYYY with complete data obtained during the study. The investigator agrees to keep in confidence all the results obtained from the study. Such information shall not be disclosed to third parties without prior written permission from YYYYYY, except to regulatory authority(ies), when requested

Individual investigators may present results of the study at scientific meetings. However prior to the submission, the *Sponsor/YYYYY* will have the opportunity to review and comment the abstracts for a period of up to 15 calendar days prior to the submission.

## 24 REFERENCES

e.g. - Vega KJ, Pina I, Krevsky B. et al. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996 Jun 1; 124 (11):980-3.

## 25 APPENDICES

Appendix 1.

Appendix 2.

Appendix 3.

Appendix 4.