

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

PROTOCOL TEMPLATE - PHASE I 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*

This document contains confidential information belonging to Sponsor. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor to use it for unauthorized purposes. In the event of actual or suspected breach of this obligation Sponsor should be promptly notified.

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.

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

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

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

TABLE OF CONTENTS

1	SYNOPSIS.....	7
2	STUDY FLOW CHART	10
3	SCHEDULE OF EVENTS.....	11
4	ABBREVIATIONS AND DEFINITIONS OF TERMS	12
5	BACKGROUND INFORMATION.....	13
6	STUDY RATIONALE.....	13
7	STUDY OBJECTIVES.....	14
7.1	PRIMARY OBJECTIVE	14
7.2	SECONDARY OBJECTIVE(S).....	14
8	STUDY ENDPOINTS.....	14
8.1	PRIMARY ENDPOINT	14
8.2	SECONDARY ENDPOINT(S)	14
9	STUDY DESIGN	14
9.1	DLT DEFINITION	14
9.2	ESCALATION SCHEMA	14
9.3	SEQUENCE OF PATIENTS ENROLLED	15
10	STUDY POPULATION	16
10.1	SUBJECT SELECTION	16
10.1.1	Subject Inclusion Criteria	16
10.1.2	Subject Exclusion Criteria	16
10.2	SCREENING FAILURES	16
10.3	REPLACEMENTS.....	16
11	ENROLLMENT PROCEDURES	16
12	STUDY TREATMENT	16
12.1	TRIAL PRODUCT (S)	16
12.2	DRUG PREPARATION (IF NOT INCLUDED IN A SPECIFIC MANUAL)	16
12.3	TREATMENT DOSE AND SCHEDULE	16
12.4	DURATION OF TREATMENT	17
12.5	DRUG ACCOUNTABILITY	17
12.6	TREATMENT DOSE MODIFICATIONS	17
12.7	CONCOMITANT MEDICATIONS AND OTHER THERAPY	17
13	SUBJECT WITHDRAWAL FROM STUDY PARTICIPATION	17
14	TREATMENT ASSESSMENT	18
14.1	PRE-TREATMENT EVALUATIONS	18
14.2	ON STUDY EVALUATIONS.....	18
14.3	OFF TREATMENT EVALUATIONS.....	18
14.4	FOLLOW-UP EVALUATIONS	18
14.5	DETAILS OF INDIVIDUAL ASSESSMENTS	18

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

14.6	PHARMACOKINETIS/PHARMACODYNAMIC/OTHER STUDIES (IF APPLICABLE).....	18
15	SAFETY ASSESSMENTS	18
15.1	PRE-EXISTING CONDITION.....	18
15.2	ADVERSE EVENT ASSESSMENT.....	18
15.3	ADVERSE EVENT REPORTING PERIOD.....	20
15.4	REPORTING PROCEDURES FOR ADVERSE EVENT	21
15.5	RECORDING ADVERSE EVENTS IN THE CASE REPORT FORMS.....	22
15.6	CAUSALITY ASSESSMENT AND GRADING OF ADVERSE EVENT SEVERITY	22
15.7	EXPOSURE IN UTERO	23
15.8	OVERDOSE.....	23
15.9	FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS	23
16	EFFICACY ASSESSMENTS	24
16.1	DEFINITION OF EFFICACY PARAMETERS	24
17	STATISTICAL METHODS	24
17.1	SAMPLE SIZE CALCULATION	24
17.2	STUDY POPULATION	24
17.3	ANALYSIS	24
17.3.1	Study Conduct and Subject Disposition.....	25
17.3.2	Baseline Characteristics and treatment Group Comparability	25
17.3.3	Treatment Analysis.....	25
17.3.4	Safety analysis.....	25
17.3.5	PK/PD analysis (or any other studies analysis).....	25
17.3.6	Efficacy analysis	25
18	QUALITY CONTROL AND QUALITY ASSURANCE	25
18.1	MONITORING	25
18.2	AUDITING	26
18.3	LABORATORY REQUIREMENTS	26
19	DATA HANDLING AND RECORD KEEPING	26
19.1	CASE REPORT FORM (CRF)	26
19.2	DATA HANDLING.....	26
19.3	RECORD RETENTION.....	26
20	ETHICAL CONSIDERATION.....	27
20.1	INSTITUTIONAL REVIEW BOARD(IRB)/ INDEPENDENT ETHICS COMMITTEE (IEC) AND COMPETENT AUTHORITY (CA)	27
20.2	ETHICAL CONDUCT OF THE TRIAL	27
20.3	INFORMED CONSENT	27
21	STUDY DISCONTINUATION CRITERIA.....	28
22	LIABILITY AND INSURANCE	28
23	CONFIDENTIALITY OF INFORMATION AND PUBLICATION OF RESULTS	28
24	REFERENCES.....	29
25	APPENDICES.....	29

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

1 SYNOPSIS

Protocol title:	<i>See note in protocol title</i>	
Protocol Number:		
IMPs:	<ul style="list-style-type: none"> • <i>Name/Code first product</i> • <i>Formulation</i> • <i>Unit strength</i> • <i>Supplier</i> 	<ul style="list-style-type: none"> • <i>Name/Code second product(if applicable)</i> • <i>Formulation</i> • <i>Unit strength</i> • <i>Supplier</i>
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"> - <i>medical need</i> - <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> - <i>summary of preclinical results (very important to report target organs for toxicities), if first time in man; summary of available clinical data.</i> - <i>doses and schedule choice rationale, only if different from standard.</i> <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. determination of MTD).</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"> • <i>Safety profile</i> • <i>Efficacy rate/Hints of activity</i> • <i>PK</i> 	
Primary Endpoint	<p><i>The endpoints are the parameters to be measured to reach the objectives (e.g. DLTs). 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"> • <i>Description of the frequency and severity of Adverse Events based on the NCI – CTCAE</i> • <i>Description of PK/PD/PG parameter</i> 	

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

Study Design	<p><i>Provide briefly a justification to explain HOW the trial will be done and define rules for the choice of starting dose in the FIH (First in Human) study and for dose increments in dose escalation.</i></p> <p><i>Describe the main methods applied to the conduct of the study:</i></p> <ul style="list-style-type: none"> <i>phase of study and setting (e.g. multicentric)</i> <i>treatment administration schedule and dose</i> <i>patients stratification (if any)</i> <i>dose escalation rules: sequence and timing of patient inclusion</i> 												
Treatment	<ul style="list-style-type: none"> <i>Route and schedule</i> <i>If combination of drugs, explain sequence of drugs (rationale)</i> 												
Escalation Scheme	<p><i>Intended dose levels e.g.</i></p> <table border="1"> <thead> <tr> <th><i>Dose Level</i></th><th><i>Drug X units</i></th><th><i>Drug Y units</i></th></tr> </thead> <tbody> <tr> <td><i>Level 1</i></td><td><i>5</i></td><td><i>10</i></td></tr> <tr> <td><i>Level 2</i></td><td><i>10</i></td><td><i>10</i></td></tr> <tr> <td><i>Level 3</i></td><td><i>15</i></td><td><i>10</i></td></tr> </tbody> </table> <p><i>Describe dose escalation rules. The following topics should be described:</i></p> <ul style="list-style-type: none"> <i>Number of patients for each cohort</i> <i>Dose Escalation process discontinuation (e.g. DE will be discontinued once the Maximum Tolerated Dose (MTD) is achieved)</i> <i>Expansion of patients at RD, and/or enrichment</i> <i>Planned interval for therapies given in cycles</i> <p><i>Suggestion:</i></p> <p><i>Leave space to include intermediate dose levels, State: "Intermediate levels may be investigated or levels can be cancelled depending on the results (toxicities, PK) observed"</i></p> <p><i>Leave flexibility to modify other parameters</i></p>	<i>Dose Level</i>	<i>Drug X units</i>	<i>Drug Y units</i>	<i>Level 1</i>	<i>5</i>	<i>10</i>	<i>Level 2</i>	<i>10</i>	<i>10</i>	<i>Level 3</i>	<i>15</i>	<i>10</i>
<i>Dose Level</i>	<i>Drug X units</i>	<i>Drug Y units</i>											
<i>Level 1</i>	<i>5</i>	<i>10</i>											
<i>Level 2</i>	<i>10</i>	<i>10</i>											
<i>Level 3</i>	<i>15</i>	<i>10</i>											
DLT / MTD / RD	<ul style="list-style-type: none"> <i>Definition of DLT</i> <i>Definition of MTD</i> <i>Definition of RD (e.g. The dose level before the MTD is the Recommended Dose)</i> <i>Consider possibility that MTD is not achieved and maximum amount of drug that can be administered (e.g. in the absence of toxicities the dose escalation has to stop at the pre-defined dose)</i> 												
Treatment Duration	<p><i>Specify the treatment duration and when a patient should be replaced.</i></p>												

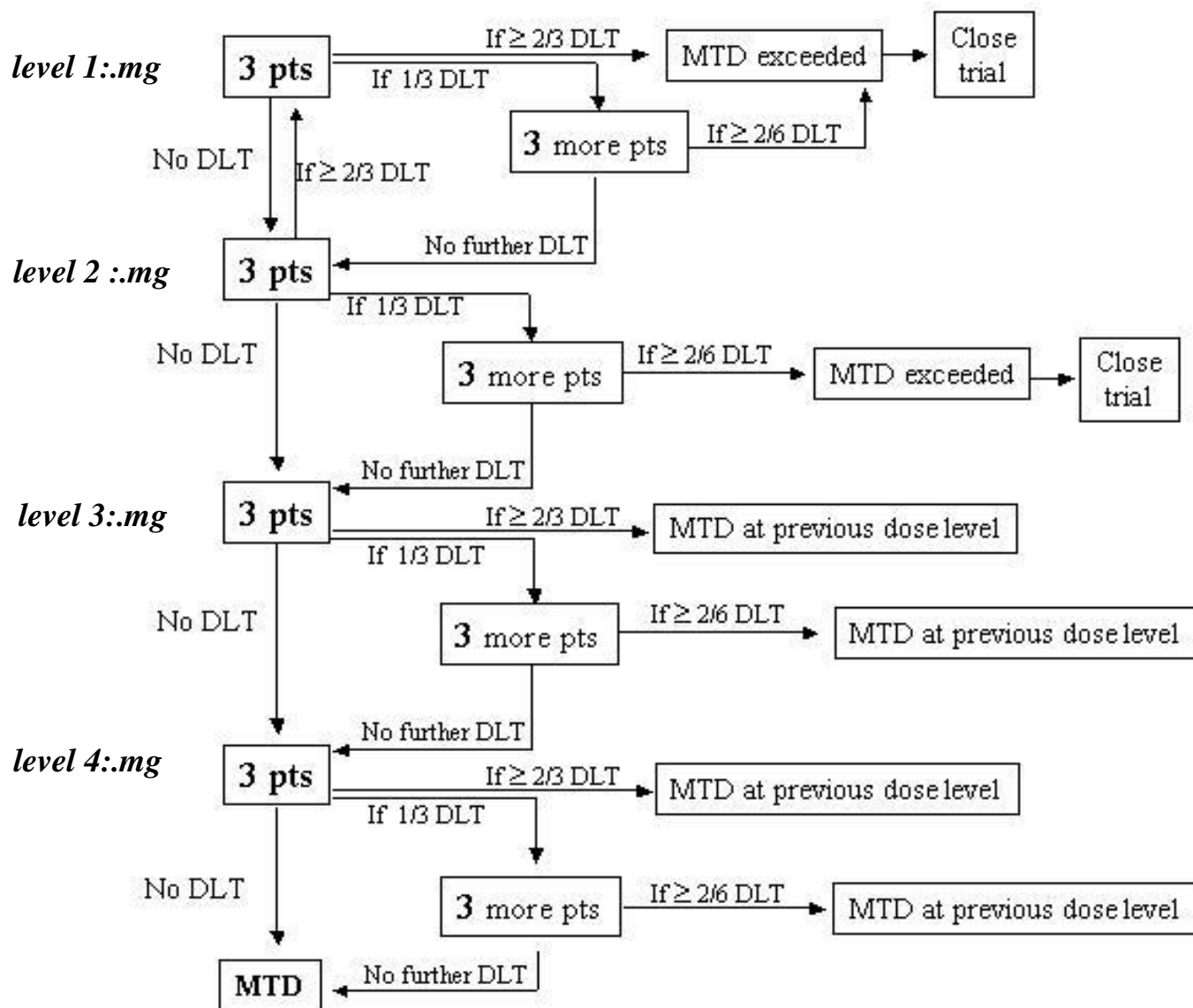
DRUG NAME/CODE
Protocol Number
Protocol Version and Date

Sequence of patient entry to dose levels	<table border="1"> <tr> <td colspan="2"><i>Sequence of patient entry to dose levels</i></td></tr> <tr> <td><i>Pts 1, 2 & 3</i></td><td><i>Simultaneously</i></td></tr> <tr> <td><i>Pt 4</i></td><td><i>4 wks after entry of 3rd pt</i></td></tr> <tr> <td><i>Pt 5</i></td><td><i>3 wks after entry....</i></td></tr> </table> <p><i>Do not forget to describe</i> <i>- if different rules concerning sequence of patients are observed in case of DLTs</i> <i>- when the subsequent cohort can be opened</i></p>	<i>Sequence of patient entry to dose levels</i>		<i>Pts 1, 2 & 3</i>	<i>Simultaneously</i>	<i>Pt 4</i>	<i>4 wks after entry of 3rd pt</i>	<i>Pt 5</i>	<i>3 wks after entry....</i>
<i>Sequence of patient entry to dose levels</i>									
<i>Pts 1, 2 & 3</i>	<i>Simultaneously</i>								
<i>Pt 4</i>	<i>4 wks after entry of 3rd pt</i>								
<i>Pt 5</i>	<i>3 wks after entry....</i>								
Supportive Therapy	<i>E.g. prophylaxis or pre-treatment. Specify dose and schedule and condition if any</i>								
Efficacy Assessments									
Safety Assessments	<i>CTC etc. 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	<p><i>There is no formal statistical calculation of sample size as only descriptive analysis will be performed.</i></p> <p><i>Indicate patient's number.</i></p> <p><i>Patients non evaluable for DLT and for safety will be replaced</i></p>								
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"> <i>Diagnosis</i> <i>Age (e.g. $\geq 18, \leq 75$,)</i> <i>Gender</i> <i>.....</i> <i>.....</i> 								
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"> <i>.....</i> <i>.....</i> <i>.....</i> <i>.....</i> <i>.....</i> 								
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>D1</i>	<i>Dx</i>	<i>Dy</i>	<i>D1</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

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

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

Urinalysis: deep stick or other

Adverse event monitoring: continuously during the study.

4 ABBREVIATIONS AND DEFINITIONS OF TERMS

To be modified according to protocol wording

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BID	bis in die/ twice a day
BSA	body surface area
BUN	blood urea nitrogen
CA	Competent Authority
CBC	complete blood count
C_{max}	maximum observed plasma drug concentration
CR	complete response
CrCl/CL _{CR}	creatinine clearance
CRA	clinical research associated
CRF (eCRF)	case report form (electronic case report form)
CTCAE	Common terminology criteria for adverse events
EC	Ethics Committee
ECG	electrocardiography, electrocardiogram
GCP	Good clinical practices
GGT	gamma-glutamyl transpeptidase
Hb	hemoglobin
ICF	Informed consent form
ICH	International Council on Harmonisation
IMP	Investigational Medicinal Product
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

<i>MTD</i>	<i>maximum tolerated dose (or dosage)</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>QA</i>	<i>Quality assurance</i>
<i>RBC</i>	<i>red blood cell</i>
<i>RD</i>	<i>Recommended Dose</i>
<i>SAE</i>	<i>Serious adverse event</i>
<i>sc</i>	<i>subcutaneous</i>
<i>SE</i>	<i>Safety evaluable</i>
<i>SOP</i>	<i>standard operating procedure</i>
<i>ULN</i>	<i>upper limit of the normal range</i>
<i>WBC</i>	<i>white blood count / white blood cells</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 non-clinical studies that potentially have clinical significance and 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)*

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

7 STUDY OBJECTIVES

7.1 Primary Objective

- *Determination of MTD*

7.2 Secondary Objective(s)

- *Safety profile*
- *Efficacy rate/Hints of activity*
- *PK/PD/PG*

8 STUDY ENDPOINTS

8.1 Primary Endpoint

- *Determination of MTD (based upon first cycle study drug related DLTs).*

8.2 Secondary Endpoint(s)

- *Description of the frequency and severity of Adverse Events based on the NCI –CTCAE V3.0*
- *Description of PK and/or PD parameter*

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 and setting: Phase I, multicenter*
- *Rules for the choice of starting dose in the FIH study and for dose increments in dose escalation.*
- *Treatment administration schedule and dose*
- *Patients stratification (if any)*
- *Dose escalation rules: sequence and timing of patient inclusion*
- *PK/PDPG studies*
- *Expected duration of subject participation*
- *Description of the sequence and duration of all trial periods, including follow-up, if any.*
- *Definition of study conclusion.*

It is important to enter all PK scheme and time of sampling. Enter also all information related to specific tests, especially if not standard to have the possibility to evaluate the feasibility

9.1 DLT definition

Provide explicit definitions of the type(s), grade(s), and duration(s) of adverse event(s) that will be considered dose-limiting.

9.2 Escalation schema

The escalating dose of XX and YY will be applied in subsequent cohorts of 3-6 patients according to the type and severity grade of acute toxicities observed during the first cycle (define n. of weeks). The dose escalation

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

process will be discontinued once the Maximum Tolerated Dose (MTD) is achieved. The dose level before the MTD is the Recommended Dose (RD); the RD will be evaluated in additional patients up to a total of Z patients.

XX and YY will be escalated according to the following rules:

- If 0 on 3 patients in each cohorts experiences dose limiting toxicities (DLTs) during the first cycle of treatment, then the next dose level will be started in a new cohort of 3 patients (no intra-patient dose escalation is allowed for determination of the MTD)
- If 1 on 3 patients experiences DLT, 3 additional patients will be treated at this dose level, and will enter the study every 2 weeks.
- If 2 or more patients in a cohort up to 6 patients develop DLT, the MTD is reached and the RD is defined. If only 3 patients had been treated at RD, further 3 patients will be enrolled and treated at this dose level to confirm the MTD.

The escalation schema could be presented with the following table

	YY mg/m ² /day	Days of YY	XX mg/m ² /wk	Days of XX	N. of patients
Level -1					
Level 1					
Level 2					
Level 3					

Do not forget to describe:

- What to do in case of DLT regarding the inclusion of other patients end the interval; e.g. "In case of DLT, it is not allowed to have more than one new patient on treatment at the same time: each new patient must enter the study just when the previous patient enrolled has finished the first cycle".
- What to do in case the MTD is not reached after having explored the levels proposed by the study protocol.

9.3 Sequence of patients enrolled

At each dose level, patients will enter according to the following sequence:

Sequence of patient entry to dose levels	
Pts 1, 2 & 3	Simultaneously
Pt 4	4 wks after entry of 3 rd pt
Pt 5	3 wks after entry....

Do not forget to describe:

- if in case of DLTs different rules concerning sequence of patients should be observed: E.g "In case of DLT, it is not allowed to have more than one new patient on treatment at the same time: each new patient must enter the study just when the previous patient enrolled has finished the first cycle".
- when the subsequent cohort can be opened

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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

Describe criteria for replacing patient (e.g. patient that does not complete cycle 1 for reason other than toxicity)

11 ENROLLMENT PROCEDURES

Before registration at study entry all patients must have given 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” and dose level, is centrally assigned by XXX.....

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)

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

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

12.4 Duration of Treatment

XXXXXX

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*
- *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.

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

14 TREATMENT ASSESSMENT

14.1 Pre-Treatment Evaluations

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

14.2 On Study Evaluations

Specify type, 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 Pharmacokinetic/Pharmacodynamic/Other Studies (If applicable)

Specify PK parameters (AUC, C_{max}, etc.) and PD evaluation.

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.

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:

- All suspected medication adverse reactions
- All reaction from medication overdose, abuse, withdrawal, sensitivity, or toxicity

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

- 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 tumor 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 (e.g. dose limiting toxicities in some phase I studies)

List any specific AE that are not to be reported and processed as SAEs even though they meet the seriousness

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

definition (e.g. expected events associated with disease progression).

15.3 Adverse Event Reporting Period

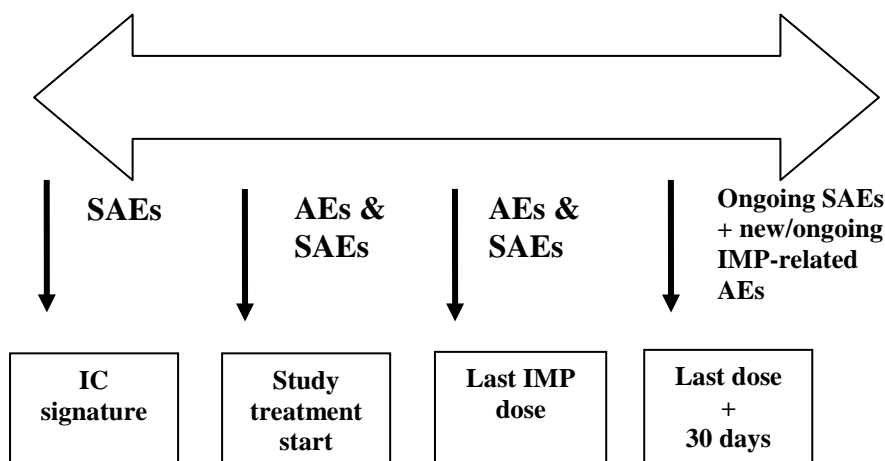
During the screening period - from informed consent signature until first IMP administration – the occurrence of any SAEs will be reported following the SAE reporting procedure described in Section 14.3.

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.



DRUG NAME/CODE
Protocol Number
Protocol Version and Date

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.

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

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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)

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,

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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](#)) [Vxxxx](#) 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.

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

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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

As this is a Phase 1b study with continued enrolment of patients until the achievement of MTD, it is not known how many patients will ultimately be enrolled. However, using the assumption that X doses will be required to reach a dose that produces dose-limiting toxicity, with 3 – 6 patients enrolled at each dose level, and at MTD up to an additional X patients will be enrolled, it is estimated that approximately Y – Z patients will be enrolled in the trial. It is anticipated that the enrolment period will be XX months.

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 First Cycle DLT evaluable population defined as those patients fulfilling the SE population criteria, and having received an adequate treatment in the first cycle to enable an appropriate evaluation of first cycle study drug related DLTs.

An evaluable patient is defined as one who has missed *no more than X doses of the IMP (specify)* within the first cycle.

In addition, any patient who experienced a drug related DLT during cycle 1 will be considered evaluable regardless of the number of doses received.

The Efficacy Evaluable (EE) population defined as all eligible 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.

17.3 Analysis

Summary statistics and analyses will be provided by dose level and where appropriate, overall. All patients who receive at least one dose *of either drug or of the combination (specify)* will be included in summary statistics. Except for study conduct and patients disposition analysis, all patients enrolled in the study will be described, even if not treated.

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

17.3.1 Study Conduct and Subject Disposition

All enrolled patients 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.

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 will be assessed through physical examinations, vital signs, laboratory tests (including serum chemistries, hematology parameters) and the recording of adverse events. Adverse events will be coded by the medical Dictionary for Regulatory Activities (MedDRA) and their severity graded according to the NCI Common terminology Criteria for Adverse Events (CTCAE) (Section 14.5). For reporting purpose the System Organ Class (SOC) and preferred term (PT) will be used. The analysis will focus on the events reported after the start of treatment (treatment emergent adverse events). Adverse event incidence by dose level and treatment period (i.e. treatment cycle 1 and the whole study period) will be calculated. In this analysis, patients will be classified according to the worst severity grade experienced during the analyzed time-window. Drug related adverse events and serious adverse events will be evaluated separately in the same way.

Hematology and biochemical toxicity will be graded according to NCI CTCAE (Section 14.5), and will be summarized in frequency distribution tables by dose level and treatment period (i.e., treatment cycle 1 and the whole study period). For each parameter, patients will be classified based on the maximal severity grade observed during the analyzed time window. Nadir values, time to nadir and time to recovery may be explored for selected haematological variables (e.g. neutrophils and platelets), based on the available laboratory assessments. Summary statistics will be presented by dose level and treatment cycle. Abnormal parameters will be documented in patient data listings.

17.3.5 PK/PD analysis (or any other studies analysis)

XXXXX

17.3.6 Efficacy analysis

Objectives responses according to RECIST criteria, will be summarized using frequencies and percentages as well as the corresponding 95% confidence interval.

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.

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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 YYYYYY and must be updated as needed by each study centre.

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

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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.

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

DRUG NAME/CODE

Protocol Number

Protocol Version and Date

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.

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 *YYYYY* 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 *YYYYY*, 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.

DRUG NAME/CODE
Protocol Number
Protocol Version and Date

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