|  |
| --- |
| Checklist: Interventional Study Protocol Diese Checkliste für die Erstellung eines Studienprotokolls dient lediglich zur Information. Gerne dürfen Sie diese Checkliste für die Erstellung Ihres Studienprotokolls nutzen. Selbstverständlich steht es Ihnen frei Ihre eigenen Dokumente zu verwenden. |
| TITLE: |  |
| PROTOCOL NUMBER: | incl. Roche number |
| VERSION NUMBER: |  |
| Eudract Number: |  |
| TEST PRODUCT(S): |  |
| AUTHOR: |  |
| SPONSOR: |  |
| DATE FINAL: |  |

|  |
| --- |
|  |
| Signatures |

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| PROTOCOL ACCEPTANCE FORM |
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**Synopsis**

|  |  |
| --- | --- |
| **TITLE** |  |
| PROTOCOL NUMBER(incl. Roche ML number) |  |
| VERSION NUMBER |  |
| EudraCT NUMBER |  |
| TEST PRODUCT |  |
| PHASE |  |
| INDICATION |  |
| SPONSOR |  |
| Objectives and Endpoints |  |
| Study Design |  |
| Description of Study |  |
| Number of Patients |  |
| Target Population, Inclusion Criteria, Exclusion Criteria |  |
| End of Study |  |
| Length of Study |  |
| Investigational Medicinal Products |  |
| Test Product (Investigational Drug) |  |
| Comparator [If Applicable] |  |
| Non-Investigational Medicinal Products[If Applicable] |  |
| Statistical Methods (Primary Analysis, Determination of Sample Size, Interim Analyses [If Applicable]) |  |

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
|  |  |

# BACKGROUND

Provide a brief description of the disease and current therapies and a brief summary of relevant trial results, relying heavily on publications to provide more detailed information.

## Background on {Condition Being Studied}

Provide a brief paragraph describing the disease and current therapies. Describe unmet needs related to the disease. If appropriate, describe issues that are relevant to patients with the disease, such as the impact of disease symptoms or current treatments on the patient. If relevant, summarize data that support biomarker or other clinical stratification.

## Background on {Test Product Name}

Provide a brief summary of findings from a) nonclinical studies that address issues of potential clinical significance that are not addressed by clinical data and b) clinical studies that are relevant to this study (including any studies that were terminated prematurely, along with reasons for premature termination).

## Study Rationale and Benefit-Risk Assessment

Provide the rationale for conducting the trial, including an integrated summary of the potential benefits and risks of the trial. If applicable, provide a rationale for the combination of two new molecular entities. Describe key areas of uncertainty for benefit or risk, any assumptions that are being made (e.g., that a surrogate is considered predictive of long-term benefit), how the trial intends to reduce uncertainty or validate assumptions, and how it is anticipated that the benefits will outweigh the risks. Describe (or refer to the protocol section that describes) risk mitigation measures (e.g., eligibility criteria, safety monitoring, definition of unacceptable toxicity).

Include references to relevant literature.

# OBJECTIVES and Endpoints

Section 2 should start off with a statement about the overall purpose of the study. This statement should include the main study endpoints and the patient population, mirroring the information found in the study title.

Subsequent sections should include objectives and endpoints categorized by efficacy, safety, biomarkers, etc. Primary and secondary endpoints must be disclosed to clinical trial registries, but disclosure of exploratory endpoints is not required.

Endpoints related to patient-reported outcomes (PROs) (or clinician-reported outcomes [ClinROs] or observer-reported outcomes (ObsROs]) should be listed under "Efficacy Objectives" or "Safety Objectives," as appropriate.

A primary objective must be designated. Each objective must be associated with at least one endpoint.

## Efficacy Objectives

The efficacy objectives can be categorized as primary, secondary, and exploratory, as applicable. PROs that evaluate efficacy should be listed as primary, secondary, or exploratory efficacy endpoints.

Primary Efficacy Objective

Secondary Efficacy Objective

Exploratory Efficacy Objective

Results from exploratory efficacy analyses must be included in the Clinical Study Report (CSR).

## Safety Objective{s} [If Applicable]

Include non-exploratory and exploratory safety objectives in this section. PROs that evaluate safety should be included in this section.

## Biomarker Objective [If Applicable]

In most cases, biomarkers endpoints should be categorized as "exploratory." However, if a pharmacodynamic (PD) biomarker is considered to be a well-established efficacy measure (e.g., viral load, LDL cholesterol), a PD biomarker endpoint may be listed in the "Efficacy Objectives" section.

## Health Status Utility Objective [If Applicable]

# STUDY DESIGN

## Description of the Study

* Include key study design features
* Indicate the scope of the trial (e.g., efficacy, safety etc.).
* Name the population to be enrolled
* Briefly describe the primary assessments used to evaluate efficacy and safety
* Specify the dosing regimen, route of administration, and duration of treatment (e.g., fixed or until progression).
* Identify and give the length of the study periods (e.g., screening, treatment, follow-up)
* Specify the number of patients and the number of treatment groups. Indicate whether patients may be replaced, and under what circumstances.
* Specify the number and location of sites.

## End of Study and Length of Study

Clearly define the "end of study" for the protocol. In many cases, last patient, last visit (LPLV, the date of the last visit of the last patient to discontinue participation in the study) can be used to define end of study. For other cases, end of study may be defined as occurrence of a certain number of events/deaths. If the end of the study is not defined by LPLV, describe and provide justification for an alternative definition. Authors should consider that the end-of-study date is used for determining the timing of required communication of study closure and the disclosure of trial results per the E.U. Clinical Trials Directive Section 4.3.2.1.

## Rationale for Study Design

In the subsections below, provide a rationale for the test product dosage and, if applicable, the patient population, control group, and biomarker assessments.

### Rationale for Control Group [If Applicable]

Provide a rationale for the type of control group.

### Rationale for Biomarker Assessments [If Applicable]

Provide a rationale for biomarker assessments. The language should be specific enough to clearly communicate the intended use of the samples.

If applicable, briefly summarize the scientific background leading to the relevant hypothesis (including references to specific data where reasonable). Explain how the hypothesis is relevant to improved patient outcome (e.g., any potential predictive value for treatment response).

### Rationale for Clinical Outcome Assessments [If Applicable]

Provide a rationale for use of any non-standard PRO (or ClinRO, ObsRO) assessments (including references that support use of the instruments).

# MATERIALS AND METHODS

## Patients

### Inclusion Criteria

### Exclusion Criteria

## Method of Treatment Assignment and Blinding

* State the method of treatment assignment and specify who will conduct the process
* Describe how the method of treatment assignment guards against systematic selection bias and ensures the comparability of treatment groups
* Describe randomization ratio, stratification factors, and use of dynamic randomization with interactive voice or web-based response system (IxRS)
* Describe unblinding procedures

### Treatment Assignment [If Applicable]

### Blinding [If Applicable]

## Study Treatment and Other Treatments Relevant to the Study Design

This section will present information regarding study treatment and other treatments that are relevant to the study design, including the following as applicable: test product, comparator (active control or placebo), and/or background therapy; premedication etc.

List all investigational medicinal products (IMPs) for this study.

### Study Treatment Formulation, Packaging, and Handling

#### {Test Product Name} {and Placebo}

Indicate who will be supplying the test product, placebo (if applicable), diluents, etc. Provide a description of the drug form (e.g., capsule, sterile liquid) and packaging. Refer the reader to the pharmacy manual, or prescribing information (as applicable) for information on formulation and handling.

#### {Second Test Product Name} [If Applicable]

If a second test product is being given, create an additional subsection for that treatment.

#### {Name of Active Control or Other Assigned Treatment} [If Applicable]

If additional treatments are assigned (e.g., active control or background therapy), include a separate subsection for each treatment.

For marketed products, formulation, packaging, and handling details that appear in the prescribing information do not need to be repeated in this section. However, any modifications (e.g., encapsulating tablets or changing packaging for blinding purposes) should be described.

### Study Treatment Dosage, Administration, and Compliance

#### {Test Product Name} {and Placebo}

* Include standard language to the effect that infusions/injections of a biologic should be given in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.
* Indicate the dose, route (e.g., oral, intramuscular, intravenous, subcutaneous), and dosing regimen.
* Describe administration methods, such as duration of infusion, injection site, setting (e.g., home, hospital), timing, relationship to meals, treatment order, post-treatment observation.
* Describe acceptable premedication, if applicable.
* Include details on assessment of compliance (if drug administration is not performed by site personnel), such as use of medication diaries or instructions for returning drug containers.

#### {Second Test Product Name} [If Applicable]

If a second test product is being given, create an additional subsection for that treatment, following instructions provided in the previous subsection.

#### {Name of Active Control or Other Assigned Treatment}[If Applicable]

If additional treatments are assigned (e.g., active control or background therapy), include dosage, administration, and compliance information for each treatment within a separate subsection.

#### {Additional Medication *[name or type (e.g., Rescue Medication)]*}[If Applicable]

Describe any additional medication that is relevant to the study design, such as challenge agents (e.g., oral tyramine, skin prick tests), agents used to assess endpoints (e.g., radiopharmaceuticals), or rescue medication, including the dose, route, and dosing regimen if appropriate.

## Concomitant Therapy {Prohibited Food, and Additional Restrictions}

### Permitted Therapy

List permitted concomitant therapies (either by name or category, such as H2-receptor antagonists). Indicate whether the dosage of any permitted concomitant therapy is required to be stable during the study. When appropriate, describe the rationale for allowing permitted concomitant therapies and explain why permitted concomitant therapies would not be expected to confound the treatment effects and how any independent effects will be evaluated. Describe whether any drug−drug interaction (including interaction with the comparator, if applicable) is expected and how any independent effects will be identified.

### Cautionary Therapy

List concomitant therapies that should be used with caution (either by name or category, such as H2-receptor antagonists).

### Prohibited Therapy

Explicitly list prohibited therapies, taking into account prescribing information for the comparator, if needed. Include the window prior to initiation of study treatment (or other reference point) during which each therapy is prohibited.

## Study Assessments

* Describe key assessments relating to safety, efficacy, immunogenicity, biomarkers, and conduct of study (e.g., compliance), including any assessments to be performed on optional samples (e.g., samples for exploratory research).
* Use appendices for very complicated assessments (e.g., "protocol‑defined asthma exacerbation" or spirometry).
* Indicate whether samples will be analyzed by a central or local laboratory. Specify laboratory assessments in detail (e.g., RBC count, hemoglobin) rather than listing only the panel name (e.g., hematology).
* If applicable, specify the order of assessments (e.g., performing PRO assessments before other assessments to reduce bias, or performing ECGs or measuring vital signs before blood draws).

Informed Consent Forms and Screening Log

Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Physical Examinations

e.g. Vital Signs, Tumor and Response Evaluations, Laboratory, Biomarker, and Other Biological Samples, Electrocardiograms

Clinical Outcome Assessments

#### Data Collection Methods for Clinical Outcome Assessments

#### Description of Clinical Outcome Assessment Instruments

For each instrument, describe the number of items, the concepts being captured, the time window for completion, and either the recall period or a statement indicating that the instrument captures the patient's current status. If there are two or more instruments, describe each instrument within a separate subsection.

## Treatment, Patient, Study, and Site Discontinuation

### Study Treatment Discontinuation

If the trial has a survival endpoint, it is important to distinguish between discontinuation from treatment and discontinuation from the study (e.g., when the patient dies, is lost to follow-up, or withdraws consent to be followed).

### Patient Discontinuation from the Study

### Study Discontinuation

List any specific requirements for study discontinuation (if applicable).

### Site Discontinuation

# ASSESSMENT OF SAFETY

## Safety Plan

This section is intended to outline the plan for managing identified and potential risks related to the study drug and other protocol-mandated therapy.

Describe the risks and how they have been identified (e.g., on the basis of mechanism of action, experience with similar molecules, and key nonclinical and clinical safety findings that are relevant to this patient population).

Discuss how the study design will address the identified and potential safety issues, including through exclusion criteria, prohibited concomitant therapy and food, special monitoring, adverse event reporting, and follow-up. Other sections of the protocol can be cross-referenced to avoid duplicating information.

Risks Associated with {Drug Name}

### Management of Patients Who Experience Adverse Events

#### Dose Modifications

Indicate whether dose modifications are allowed. If allowed, describe dose modification rules, including possibility for escalating the dose after a dose reduction.

#### Treatment Interruption

Describe treatment interruption and discontinuation rules (e.g., maximum amount of time treatment can be withheld) for study treatments.

#### Management Guidelines

Describe recommended medical management of patients who experience specific adverse events, including guidelines for dosage modification and treatment interruption or discontinuation.

#### Management of Increases in QT Interval [If Applicable]

## Safety Parameters and Definitions

#### Adverse Events

#### Serious Adverse Events

#### Adverse Events of Special Interest

## Methods and Timing for Capturing and Assessing Safety Parameters

#### Adverse Event Reporting Period

The duration of the post-treatment follow-up period for safety surveillance purposes should be based on the known PK and PD properties of the test product. This may be influenced by such things as the half-life of and previous experience with the test product. In the absence of specific delayed-toxicity concerns or safety hypotheses, the following guidelines can be used to determine the length of the post-treatment follow-up period:

|  |  |  |
| --- | --- | --- |
|  | Small Molecules | Large Molecules |
| Single-dose studies | 5 elimination half-lives or 14 days after the final dose, whichever is longer | 2 elimination half-lives or 28 days after the final dose, whichever is longer |
| Multiple-dose studies | 5 elimination half-lives or 28 days after the final dose, whichever is longer | 2 elimination half-lives or 28 days after the final dose, whichever is longer |

#### Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints.

#### Assessment of Severity of Adverse Events

There are three table options to select from for adverse event grading: the NCI CTCAE, the World Health Organization (WHO) toxicity scale, and a mild/moderate/severe schema.

#### Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

* Temporal relationship of event onset to the initiation of study drug
* Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
* Known association of the event with the study drug or with similar treatments
* Known association of the event with the disease under study
* Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
* Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

#### Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### {Infusion-Related} [or] {Injection} Reactions [If Applicable]

#### Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events.

#### Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF.

#### Abnormal Laboratory Values

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

#### Abnormal Vital Sign Values

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

#### Abnormal Liver Function Tests

#### Deaths

All events with an outcome or consequence of death should generally be classified as serious adverse events and reported to the Sponsor immediately.

#### Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

#### Hospitalization or Prolonged Hospitalization

Additional language may be needed depending on the trial. For example, some events that require hospitalization may be reported as adverse events rather than serious adverse events.

#### Cases of Accidental Overdose or Medication Error

#### Patient-Reported {or Observer-Reported} Outcome Data [If Applicable]

#### Safety Biomarker Data [If Applicable]

## Immediate Reporting Requirements from Investigator to Sponsor

Emergency Medical Contacts:

Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

#### Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

#### Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until {XX} after the final dose of study drug.

### Reporting Requirements for Pregnancies

#### Pregnancies in Female Patients

#### Pregnancies in Female Partners of Male Patients [If Applicable]

Follow-up on partner pregnancies may be required for some IMPs.

#### Abortions

#### Congenital Anomalies/Birth Defects

### Reporting Requirements for Medical Device Complaints [If Applicable]

## Follow-Up of Patients after Adverse Events

Each adverse event should be followed up until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent.

## Adverse Events That Occur after the Adverse Event Reporting Period

# STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

* Explicitly define analysis populations for efficacy and safety (explicit to the analysis time), including treatment group allocations (according to intended treatment vs. treatment received).
* Explicitly describe criteria that determine when analyses will occur (e.g., data cutoff date when a targeted number of investigator-assessed events has occurred, or minimum follow-up after last patient enrolled). Provide similar information for any additional analyses intended to support labeling (e.g., a mature overall survival analysis well after a primary PFS analysis).
* Indicate how type I error control for multiplicity will be managed, or indicate that this will be described in the Statistical Analysis Plan (SAP).
* Describe the plan for a structured benefit-risk analysis, if applicable.
* Indicate additional global considerations such as the following:
* Hypothesis tests will be two-sided unless otherwise indicated.
* Details of the analyses will be provided in the SAP.

## Determination of Sample Size

## Summaries of Conduct of Study

* List the variables that will be summarized to determine whether the integrity of the study was maintained, such as enrollment, study drug administration, major protocol deviations, integrity of the blind, and other data that have an impact on the general conduct of the study.
* Describe the sources of data that will be used to assess study conduct (e.g., screening log, clinical database, monitoring reports) and the data that will be used from each.
* Indicate that descriptive statistics will be used in evaluating the conduct of the study.

## Summaries of {Treatment Group Comparability} [or] {Demographic and Baseline Characteristics}

## Efficacy Analyses

### Primary Efficacy Endpoint

### Secondary Efficacy Endpoints

### Exploratory Efficacy Endpoints

## Safety Analyses

* List all safety endpoints
* Indicate the patient groups (usually all patients) to be used in analyzing the safety variables.
* Describe methods for assessing, recording, and analyzing safety variables.
* Carefully define the time windows of adverse event onset that will be considered.

Include subheadings only for studies with exploratory safety endpoints:] e.g. Analyses of Exposure, Adverse Event, Laboratory, Vital Sign, Immunogenicity Analyses [If Applicable]

## Biomarker Analyses [If Applicable]

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

## Interim {Analysis} [or] {Analyses}

It is strongly advised that all studies allow for optional interim analyses.

# DATA COLLECTION AND MANAGEMENT

## Data Quality Assurance

## Electronic Case Report Forms

## Electronic Patient- {and Clinician- [and/or Observer-]} Reported Outcome Data [If Applicable]

## Source Data Documentation

Before study initiation, the source documents that will need to be examined during monitoring visits to validate critical protocol data elements should be prospectively determined.

## Retention of Records

# ETHICAL CONSIDERATIONS

## Compliance with Laws and Regulations

## Informed Consent

## Institutional Review Board or Ethics Committee

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

# STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

## Study Documentation

## Protocol Deviations

## Management of Study Quality

## Site Inspections

## Protocol Amendments

Per 21 CFR 312.30(b), a protocol amendment is warranted when a change significantly affects the safety of patients or (for Phase II or III) affects the scope of the investigation or the scientific quality of the study. Per the EC Clinical Trials Directive, a protocol amendment is warranted when changes are substantial and are likely to have an impact on the safety of the trial patients or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant.

# REFERENCES