This guide/electronic template is designed for writing the statistical analysis plan (SAP) for Phase II, III, IV studies and early phase oncology studies. For late phase studies, this template is primarily oriented toward confirmatory efficacy and safety trials, with text designed for adequate and well-controlled efficacy studies: text should be appropriately adapted for studies with a different design.

Instructions for completing the individual sections of the SAP are given section by section. The order of the endpoints should be aligned with the hierarchy of the study objectives. In this template, “randomized” or “enrolled” (or “exposed”) is to be used according to whether the study is a randomized or a non-randomized study.

The following general points should be noted (starting from next Title Page):

* Instructional text (ie, text providing guidance) is displayed in orange highlighted text. This text should not appear in the final version but should be considered when designing/writing the section.
* Common text: black font preceded by <Start of common text> and followed by <End of common text> is common language intended to be harmonized across studies. The recommendation is to use this text as written to maintain consistency across template users, but the text can be adapted if required.
* Suggested text: black font preceded by <Start of suggested text> and followed by <End of suggested text> is the suggested language to be used and can be deleted/modified as needed.
* Example text: black font preceded by <Start of example> and followed by <End of example> is example text and should be removed by the author.
* Variable text: pink text is the variable text that should be addressed based on individual study need.

|  |  |
| --- | --- |
| [Statistical Analysis Plan](#ToC) | |
| Protocol title: | Title |
| Protocol number: | Protocol number |
| Compound number (INN/Trademark): | Compound number  INN/Trademark |
| Study phase: | Study Phase |
| Short Title: | Protocol brief title  Acronym |
| Statistician: | last name, first name (contractor, xxx) |
| Statistical project leader: | last name, first name |
| Date of issue: | dd-Mmm-YYYY |
| Regulatory agency identifier number(s): | |
| **IND:** | regulatory agency identification number as appropriate |
| **EudraCT/EU-trial number:** | regulatory agency identification number as appropriate |
| **NCT:** | regulatory agency identification number as appropriate |
| **WHO:** | Universal Trial Number (UTN) identification number |
| **EUDAMED:** | regulatory agency identification number as appropriate |
| **Other:** | regulatory agency identification number as appropriate |

|  |  |  |  |
| --- | --- | --- | --- |
| Date: | dd-Mmm-YYYY | Total number of pages: | 3 |

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Version history

The statistical analysis plan (SAP) history table gives the timing, rationale, and key details for the major changes to the statistical analysis features in the SAP. It includes, the major changes (if any) in SAP version 1.0 from the most recent approved protocol, and the major changes in SAP later versions comparing to previous SAP version.

The changes to the principal features of the analysis, with rare exception, require a protocol amendment (ICH E9) and should not be implemented solely by an SAP change. “Principal features of the analysis” encompass the confirmatory aspects of the trial, including the primary endpoints/analyses, and the analysis populations associated with these analyses.

The major changes to the statistical analysis features from a protocol version to another are to be described under Section 3.9.

<Start of suggested text for early phase oncology studies and late phase studies with only one study part >

This statistical analysis plan (SAP) for study Protocol number is based on the protocol dated dd-mmm-yyyy. [There are no major changes to the statistical analysis features in this SAP/This section summarizes the major changes to the statistical analysis features in the SAP].

Please choose one of the sentences below to describe the timing of the SAP in relation to FPI and interim analyses.

This SAP is approved before the first participant is [enrolled/randomized]. If the (amended) SAP is approved before FPI

The first participant was [enrolled/randomized] on dd-mmm-yyyy. If the (amended) SAP is approved after FPI and no IA is planned

The first participant was [enrolled/randomized] on dd-mmm-yyyy. This SAP is approved before the first interim analysis is conducted. If the (amended) SAP is approved after FPI but before first IA

The first participant was [enrolled/randomized] on dd-mmm-yyyy. The first interim analysis was performed on dd-mmm-yyyy. If the amended SAP is approved after first IA (initial version of SAP should be approved before first IA)

<End of suggested text for early phase oncology studies and late phase studies with only one study part >

<Start of suggested text for early phase oncology studies with dose escalation (or safety run-in) and dose expansion study parts >

This SAP is approved before the first participant is enrolled in dose escalation part. If the (amended) SAP is approved before FPI of dose escalation part

The first participant was enrolled in dose escalation part on dd-mmm-yyyy. This SAP is approved before the first participant is [enrolled/randomized] in the expansion part. If the (amended) SAP is approved after FPI of dose escalation but before FPI of dose expansion

The first participants in dose escalation and dose expansion were enrolled on dd-mmm-yyyy and dd-mmm-yyyy, respectively. If the (amended) SAP is approved after FPI of dose expansion and no formal IA is planned

The first participants in dose escalation and dose expansion were enrolled on dd-mmm-yyyy and dd-mmm-yyyy, respectively. This SAP is approved before the first interim analysis is conducted in the expansion part. If the (amended) SAP is approved after FPI of dose expansion part but before the first formal IA (it is recommended to have the SAP approved before first formal IA of the dose expansion part or at least before DBL).

The first participant in dose expansion was [enrolled/randomized] on dd-mmm-yyyy. The first interim analysis was performed on dd-mmm-yyyy. If the (amended) SAP is approved after first formal IA of the expansion part

<End of suggested text for early phase oncology studies with dose escalation and dose expansion parts >

<Start of suggested text >

Major changes in statistical analysis plan

| SAP Version | Approval Date | Changes | Rationale |
| --- | --- | --- | --- |
| 1 | dd-mmm-yyyy | Not Applicable  Or list major changes (if any) in SAP version 1.0 from most recent protocol at the time of SAP version 1.0. | Original version |
| 2 (if apply) | dd-mmm-yyyy | List major changes in SAP version 2.0 from SAP version 1.0 |  |
| … |  |  |  |

<End of suggested text>

<Start of example>

This Statistical Analysis Plan (SAP) for study Protocol number is based on the protocol dated dd-mmm-yyyy. This section summarizes major changes to the statistical analysis features in the SAP. This SAP is approved before the first participant is [enrolled/randomized].

Major changes in statistical analysis plan

| SAP Version | Approval Date | Changes | Rationale |
| --- | --- | --- | --- |
| 1 | 03-Sep-2009 | Not Applicable | Original version |
| 2 | 03-Mar-2010 | Primary analysis changed from unstratified log-rank to log-rank stratified by center (randomization stratification factor). | Per FDA’s recommendation. |
|  |  | The fasting glucose criterion is included in the definition of “New onset of diabetes” (see Section 3.7.3). | Per FDA’s recommendation. |
| 3 | Current version | The analysis of sub-components of the primary efficacy endpoint (DVT of upper limb, proximal DVT of lower limb, distal DVT of lower limb, symptomatic non-fatal PE and PE detected by tumor evaluation) is added | To further investigate the consistency of the results between the different components. |

<End of example>

# introduction

Indicate if major changes to protocol-planned analyses exist, and if so, reference the SAP section documenting these changes. If there are no major changes to the analyses described in the protocol, include a statement to address this information.

<Start of common text>

[Major changes to the protocol-planned analyses are described in [Section](#_Ref77689393) 3.9. /There are no major changes to the analyses described in the protocol.]

<End of common text>

## Study design

Describe the study design and randomization (if applicable), consistent with the protocol. Recommend not duplicating information already in the protocol schedule of activities.

Items to consider:

* Study phase, study population, study duration, design type [eg, parallel, crossover, factorial, single group, sequential multiple assignment randomized trial (SMART)], and other design elements as required (eg, dose-escalation, multicenter, adaptation). For dose escalation methodology, be very brief and do not repeat all the details already included in the protocol. Exception: in case a modification of the dose escalation methodology is not documented in the protocol (eg, modification of the prior), mention this modification in the SAP.
* Control method [eg, placebo, active comparator, low dose, historical, or none (ie, uncontrolled)].
* Blind level [eg, open-label, single-blind, double-blind, double-blind (sponsor unblinded), matching placebos, double-dummy, etc].
* Method of assignment to intervention and randomization scheme including randomization ratio, stratification (if applicable). However, randomization block size information should not be revealed in the SAP.
* Description of any provisions for extending the study or entry to roll-over studies.
* Rules/procedures for dose changes/adjustments including flexible dosing; dose reductions, interruptions, tapering, or rescue as applicable.

<Start of example (adapted from a multiple sclerosis study)>

This is a long-term multicenter, multinational, randomized, placebo-controlled, double-blind, 3‑parallel-group, stratified study.

After a screening phase of up to 2 weeks, participants will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1:1 ratio to 1 of the 3 intervention groups (dose 1, dose 2 and placebo) and treated double-blind for approximately 2 years. Randomization will be stratified by investigative site and baseline EDSS score (≤3.5 versus >3.5). Approximately 462 participants (154 participants per intervention group) will be randomized from approximately 20 sites.

Study primary analysis will be conducted after study completion.

<End of example>

<Start of example (for early phase oncology studies with dose escalation and dose expansion parts)>

This is an open-label, nonrandomized, dose escalation and dose expansion study.

* Dose escalation: The starting dose is xx and the dose levels indicated in Table 1 are planned to be investigated. Dose escalation will proceed using [3+3, BLRM, mTPI2, …]. Intermediate dose levels may be investigated.

Table 1 - Dose levels in dose escalation part

| Dose Level | Dose |
| --- | --- |
| DL1 | xx mg |
| … | … |
|  | |

* Dose expansion: Participants enrolled in the dose expansion part will receive Compound number at the recommended phase 2 dose (RP2D) determined at the end of dose escalation.

<End of example (for early phase oncology studies with dose escalation and dose expansion parts)>

## objectives and endpoints

The objectives and their corresponding endpoints will be copied from the protocol and should be identical to protocol language.

<Start of common text>

Table 2 - Objectives and endpoints

| Objectives | Endpoints |
| --- | --- |
| Primary | |
| * Insert library content here if available | * Insert library content here if available |
| Secondary | |
| * Insert library content here if available | * Insert library content here if available |
| [Tertiary/Exploratory/Other] | |
| * Insert library content here if available | * Insert library content here if available |

|  |
| --- |
|  |

Will be imported from protocol in case of several objectives and endpoints tables in the protocol

Enter other objectives and endpoint tables

<End of common text>

### Estimands

Implementation of estimands is highly recommended for pivotal studies. Please remove this section if estimands are not implemented in the study. For early phase oncology studies, it is recommended to implement estimands for key efficacy endpoints (eg, ORR, or DOR/PFS if needed) of the expansion part. The implementation of estimands is not recommended for primary safety endpoints (eg, DLT, Infusion rate).

In the protocol, the recommendation is to include clear definition and detailed specifications on estimands for the primary endpoint (primary analysis and potentially main sensitivity analysis) and for a key secondary endpoint if important for a claim (eg, overall survival in oncology studies). High level information about missing data handling is enough for the protocol.

Estimands include the five following attributes: the analysis population, the endpoint, how to account for intercurrent events (such as intervention discontinuation, initiation of rescue medication, study discontinuation), the population-level summary (including missing data handling) and the treatment condition (ie, intervention of interest and comparator). The possible intercurrent event handling strategies include, but not limited to,

* **Treatment policy**: the analysis will be performed regardless of intercurrent events to estimate the treatment effect in a pure “ITT” setting. Analyses will generally use all data collected regardless of intercurrent events and missing data imputations will generally be done considering the timing of the missing data in relation to the intercurrent events.
* **Hypothetical**: the analysis will be performed under a theoretical scenario (eg, had study intervention not been discontinued, had background therapies not been modified) to estimate what would have been the treatment effect had the theoretical scenario occurred. Analyses will generally exclude data collected after the intercurrent events. Missing data imputations/post-intercurrent event data replacement will generally be done under the hypothesis of no intercurrent event.
* **Composite**: the endpoint definition includes the intercurrent event (eg, participant being considered as non-responder in case a rescue medication is initiated).
* **While on-treatment**: the analysis will be performed on the measurements up to the time of the treatment discontinuation. Terminology for this strategy will depend on the intercurrent event of interest (eg, “while not initiating rescue therapy” when considering the initiation of rescue therapy as an intercurrent event). Like the Composite strategy, the while on treatment strategy can be thought of as impacting the definition of the variable, in this case by restricting the observation time of interest to the time before the intercurrent event.

The estimands should be clear and include specification on each attribute. Define one or more estimands for the primary and key secondary objectives. If including more than one estimand for the primary objective, one of them should be identified primary. If for a particular study different primary estimands/endpoints are required for different regulatory authorities, it is recommended to specify which one is considered primary for each regulatory authority.

The primary estimand of primary and secondary endpoints where a label claim is targeted are to be summarized in below Table 3 with information on each attribute, and fully detailed in [Section](#_Ref59094469) 3. Sensitivity analyses (using different estimators for the same estimand) and supplementary analyses (targeting a different estimand, for example based on a different population than the one used in the primary estimand) are not to be included in Table 3 and should be detailed in [Section](#_Ref59094469) 3. Safety endpoints will generally not be included in Table 3.

Treatment condition is to be included in the text if common to all estimands, or to be specified in the “endpoint” column otherwise. For analysis model and missing data handling, high level information is to be included in Table 3 and full details in [Section](#_Ref59094469) 3. The additional derivation details of the endpoints, if any, should be provided in the corresponding subsections of [Section](#_Ref59094469) 3.

A name/identifier for the estimands (for example using the terminologies for intercurrent event handling strategies) should be included in the table, if possible, to facilitate re-use throughout the SAP.

<Start of suggested text>

Primary estimand defined for main endpoints are summarized in below Table 3. More details are provided in [Section](#_Ref59094469) 3.

For all these estimands, the comparison of interest will be the comparison of Compound number vs. control.

Table 3 - Summary of primary estimand for main endpoints

| Endpoint Category (estimand) | Estimands | | | |
| --- | --- | --- | --- | --- |
| Endpoint | Population | Intercurrent event(s) handling strategy | Population-level summary  (Analysis and missing data handling) |
| **Primary objective: XXX** | | | | |
| Primary endpoint (estimand name/id) | Change from baseline in <clinical variable 1> <to timepoint> | ITT | Initiation of rescue medication: “had rescue medication not been initiated” (hypothetical)  Discontinuation of intervention: “regardless of intervention discontinuation (treatment policy) | Mean difference between interventions from analysis of covariance (ANCOVA). Missing data imputed with multiple imputation using post-treatment data of participants from same randomized arm |
| [Secondary endpoint (estimand name/id) |  |  |  |  |
| **Secondary objective: XXX** | | | | |
| Secondary endpoint (estimand name/id) |  | ITT |  |  |

<End of suggested text>

<Start of example 1 (continuous endpoints)>

Table 4 - Summary of primary estimand for main endpoints

| Endpoint Category (estimand) | Estimands | | | |
| --- | --- | --- | --- | --- |
| Endpoint | Population | Intercurrent event(s) handling strategy | Population-level summary (Analysis and missing data handling) |
| **Primary objective: to demonstrate the reduction of low density lipoprotein cholesterol (LDL-C) of** Compound number **as add-on therapy to stable maximally tolerated daily statin therapy with or without other lipid modifying therapy in comparison with placebo in participants with heterozygous familial hypercholesterolemia.** | | | | |
| Primary endpoint  (Estimand 1) | Percent change from baseline in LDL-C to Week 24 | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) | Mean difference between interventions from ANCOVA. Missing data imputed with pattern mixture modela. |
| Secondary endpoint (Estimand 1) | Percent change from baseline in LDL-C to Week 12 | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) | Mean difference between interventions with ANCOVA. Missing data imputed with pattern mixture modela |
| Secondary endpoint (Estimand 2) | Percent change from baseline in LDL-C to Week 24 | Randomized and treated | Regardless of lipid modifying therapies (treatment policy strategy) / had study intervention not been discontinued (treatment policy strategy) | Mean difference between interventions with MMRM. Missing data being handled by MMRM under MAR. |
| **Secondary objective: To evaluate the effect of** Compound number **on other lipid parameters (ie, Apo B, non-HDL-C, total-C, Lp (a), HDL-C, triglycerides (TG), and Apo A-1 levels.** | | | | |
| Secondary endpoint (Estimand 1) | Percent change from baseline in Apo-B to Week 24 | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) | Mean difference between interventions with ANCOVA. Missing data imputed with pattern mixture modela. |
|  | | | | |
| 1. Missing data during the on-treatment period imputed under Missing-At-Random (MAR). Missing data during post-treatment period imputed based on participant’s own baseline value | | | | |

<End of example 1>

<Start of example 2 (survival endpoints)>

Table 5 - Summary of primary estimand for main endpoints

| Endpoint Category (estimand) | Estimands | | | |
| --- | --- | --- | --- | --- |
| Endpoint | Population | Intercurrent event(s) handling strategy | Population-level summary (Analysis and missing data handling) |
| **Primary objective: to compare the effect of** Compound number **with placebo on the occurrence of MACE in participants with recent ACS** | | | | |
| Primary endpoint  (Estimand 1) | Time from randomization to first occurrence of MACE | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) / Had study not been discontinued (hypothetical strategy) | Hazard ratio from Cox model. P-value from log-rank test. Participants will be censored at the common study end date (CSED) or at the date of last contact when information on CV events (presence or absence) has been retrieved, whichever comes first. |
| Secondary endpoint (Estimand 1) | Time to recurrent MACE | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) / Had study not been discontinued (hypothetical strategy) | Hazard ratio and p-value from Andersen-Gill mean intensity model. Participants will be censored at the CSED or at the date of last contact when information on CV events (presence or absence) has been retrieved, whichever comes first. |
| **Secondary objective: to compare the efficacy of** Compound number **versus placebo on secondary endpoints (any CHD event and all-cause mortality)** | | | | |
| Secondary endpoint (Estimand 1) | Time from randomization to first occurrence of any CHD event | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) / had study not been discontinued (treatment policy strategy) | Hazard ratio from Cox model. P-value from log-rank test. Participants will be censored at the CSED or at the date of last contact when information on CV events (presence or absence) has been retrieved, whichever comes first. |
| Secondary endpoint (Estimand 1) | Time from randomization to all-cause mortality | ITT | Regardless of lipid modifying therapies (treatment policy strategy) / regardless of adherence to study intervention (treatment policy strategy) / had study not been discontinued (hypothetical strategy) | Hazard ratio from Cox model. P-value from log-rank test. Participants will be censored at the CSED or at the date of last contact, whichever comes first. |
|  | | | | |

<End of example 2>

<Start of example 3 (oncology)>

Table 6 - Summary of primary estimand for main endpoints

| Endpoint Category (estimand) | Estimands | | | |
| --- | --- | --- | --- | --- |
| Endpoint | Population | Intercurrent event(s) handling strategy | Population-level summary  (Analysis and missing data handling) |
| **Primary objective: to determine whether** Compound number **improves the progression free survival (PFS) when compared to placebo in participants with XXXX.** | | | | |
| Primary endpoint (Estimand 1) | PFS | ITT | Had new anticancer therapy not been initiated (hypothetical strategy)  Regardless of IMP discontinuation (treatment policy strategy)  Had two or more consecutive tumor assessments not been missed/unevaluable immediately before documented progression or death (hypothetical strategy) | Hazard ratio (HR) between two intervention arms, estimated using Cox proportional hazard model stratified by randomization stratification factors. The primary comparison will be performed using log-rank test stratified by randomization stratification factors. |
| **Secondary objective: to assess other indicators of antitumor activity.** | | | | |
| Secondary endpoint (Estimand 2) | Objective response | ITT | While not initiating new anticancer therapy strategy.  Regardless of IMP discontinuation (treatment policy strategy) | ORR, defined as the percentage of the participants with objective response (CR or PR) as best overall response. The 90% CI using Clopper Pearson methods.  To be adapted if needed (eg, ORR is CR, VGPR and PR in multiple myeloma) |

<End of example 3>

# Analysis populations

The information will be copied from the protocol. Additional analysis populations may be added. The most commonly used analysis populations are given as examples below. Select only those applicable to the study. For early phase oncology studies with both escalation and expansion parts, do not duplicate the populations for both parts, the defined populations will be applicable to both parts, unless otherwise specified.

If necessary, reference any team decisions that impact participant exclusions, for example, if sites are excluded because of GCP violations. Such decisions can be documented in the meeting minutes and in the CSR if they are made after SAP finalization.

<Start of suggested text>

The following populations for analyses are defined. Unless otherwise specified, these populations will be applicable for both dose escalation and dose expansion parts. The participants included in the dose escalation part, if fulfilling the inclusion criteria of the expansion part and if the planned dose and dosing schedule are the same as in dose expansion will be included in the analyses of dose expansion.

Table 7 - Populations for analyses

| Population | Description |
| --- | --- |
| Screened | All participants who signed the ICF. |
| Randomized | All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received or not.  For non-randomized studies, enrolled population or exposed population (defined below) may be used instead. |
| Exposed (Applicable for non-randomized studies) | All screened participants who have taken at least 1 dose of study intervention, regardless of the amount of treatment administered. |
| Enrolled (Applicable for non-randomized studies) | All participants from screened population who have been allocated to an intervention by IRT regardless of whether the intervention was received or not. |
| Intent-to-treat (ITT) | All [randomized/enrolled/exposed] participants.  Participants will be analyzed according to the intervention allocated by randomization.  For randomized studies, “randomized” is to be used. |
| Modified ITT (mITT) | All participants from ITT population who takes at least 1 dose of study intervention and with an evaluable primary endpoint.  The primary endpoint is evaluable when the following conditions are met:  to be completed  Participants will be analyzed according to the intervention allocated by randomization. |
| Per-protocol (PP) | All participants from [ITT, mITT] population who…  Participants will be analyzed according to the intervention they actually received.  In general, per-protocol analysis should not be pre-specified in adequately controlled, potentially pivotal studies, which generally should use an ITT or mITT analysis as the only analysis for the primary objective. In the cases that a per-protocol population is defined (eg, in non-inferiority studies), the criteria to define the per-protocol population should be clearly pre-specified in the SAP. |
| Population without trial impact (disruption) due to COVID-19 | All [randomized/enrolled/exposed] participants:   * without any critical or major deviation related to COVID-19 * and who did not permanently discontinue treatment due to COVID-19 * and who did not permanently discontinue study due to COVID-19. |
| Efficacy population (Applicable for early phase oncology single arm studies) | All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment. Note: the objective of this definition is only to exclude participants “newly” enrolled as compared to the cut-off date. This will apply to analyses conducted while the enrolment is ongoing. For all other analyses, this definition will lead to include all exposed participants. |
| Response evaluable population (Applicable for early phase oncology studies) | All participants from the [safety/exposed] population with measurable disease at baseline, an evaluable baseline and at least one evaluable post-baseline tumor assessment. Participants who died from disease progression before any TA will also be response-evaluable. This population is not recommended for primary analysis that should rather be performed on the efficacy population. |
| Safety | All [enrolled/randomized] participants who have taken at least 1 dose of study intervention, regardless of the amount of treatment administered.  Participants will be analyzed according to the intervention they actually received.  For randomized studies, “randomized” is to be used.  It is recommended not to include this population for early phase oncology single-arm studies if the exposed population is defined. |
| DLT-evaluable (Applicable for early phase oncology studies) | All participants who have been observed for at least XX days and have received at least YY% of the intended [Cycle 1/Cycle 1 and 2] dose of [IMP/each IMP]. Any participant who experienced a DLT during that period will also be DLT-evaluable. Choose YY (eg, 90%) according to the type of drug, the administration schedule and the defined dose levels. |
| Pharmacokinetic (PK) | All participants from the [safety/exposed] population with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times.  Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they actually received.  For randomized studies, “randomized” is to be used. |
| Pharmacodynamics (PDy) | All participants from the [safety/exposed] population with at least one post-baseline PDy parameter assessed. |
| PK/PD inclusion of this population in the SAP generally not recommended but can be included if needed after discussion with PK/PD function | All participants included in both the PK and the PD populations. In addition, participants included in the PD population and having received only placebo will be part of the PK/PD population.  To be adapted to study specificities, for example based on time-matched PK and PD data “All participants included in both the PK and the PD populations with at least 1 PK time point with a PD measure performed within 30 minutes of a PK time point". Exclusion of some study intervention group might also apply.  Name of the population and definition to be adapted for concentration-QT analyses. |
| ADA | All participants from the [safety/exposed] population treated with Compound number with at least one post-baseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.  For randomized studies, “randomized” is to be used. ADA results from control intervention (eg, placebo) are not to be included in the analyses unless the control intervention is a biosimilar for which the same ADAs as the SARxxxxxx are measured (with the same assay) or the control intervention have different ADAs that are measured (in such case analyses will be done separately across interventions). The population definition is to be adapted if such intervention is used as comparator. Other ADA populations may be defined in case of combination intervention. |
| Open-label extension (OLE) | All participants who received at least one dose of intervention during the open-label extension phase.  For studies with 2 phases, one double-blind phase followed by an open-label phase (OLE) in which all participants receive the tested intervention, it is recommended to define a single population in which all the analyses (efficacy, safety etc) of the open-label extension phase (analyzed separately or combined with the double-blind phase) will be conducted, rather than duplicating all the populations for both double-blind and OLE phases. |

<End of suggested text>

<Start of common text>

Participants exposed to study intervention before or without being [enrolled/randomized] will not be considered [enrolled/randomized] and will not be included in any analysis population. The safety experience of these participants will be reported separately.

[Enrolled/Randomized] participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the [safety/exposed] population as randomized.

For any participant [enrolled/randomized] more than once, only the data associated with the first [randomization/enrollment] (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later [randomization/enrollment] will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the intervention group as randomized if the participant received at least one administration as randomized.

<End of common text>

# Statistical analyses

Refer to QSD-002873 Standard Statistical Outputs Templates for the layout of the standard statistical outputs.

Listings are generally not to be mentioned in the SAP. However, keep in mind that some listings might be needed for submission in specific regions.

## General considerations

The information will be copied from the protocol. Additional general considerations may be added.

This section describes general methods and definitions that do not need to be repeated in the subsequent sections. Suggested topics to be included in this section, if applicable to the study, are provided below.

* Describe when the primary analysis will be performed. Describe the timing of the final analysis if there will be subsequent reporting events, eg, after long term follow-up.
* Decision criteria, such as nominal significance levels, 1- or 2-sided tests, and confidence interval probabilities
* Common definitions of baseline.
* General methods (eg, how the continuous variables will be summarized)
* Handling of wrong stratification (eg, if statistical model plans for adjustment on stratification factors, specify whether stratification factors per IRT or per eCRF will be used)
* General choice of populations for analyses
* Treatment grouping strategy eg, combining all active dose arms versus control. For studies with several parts (eg, dose escalation and dose expansion for early phase oncology studies, double-blind and open-label periods for late phase studies), provide treatment group strategy for all parts.
* Definition of observation periods

<Start of common text>

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of double-blind investigational medicinal product (IMP). For participants [enrolled/randomized] but not treated, the baseline value is defined as the last available value before [randomization/enrollment].

Unless otherwise specified, analyses will be performed by [intervention group/dose level] (and overall for baseline and demographics characteristics).

<End of common text>

<Start of example text for early phase oncology studies with dose escalation and dose expansion parts >

Unless otherwise specified, analyses will be performed separately for dose escalation and dose expansion.

* In dose escalation part, analyses will be presented by dose level and overall (except for PK analyses). Unless otherwise specified, analyses will be based on the intended dose level at C1D1.
* For studies with a single tumor type/indication and a single dose/regimen. In dose expansion part, unless otherwise specified, analyses will be performed overall. Participants included in the dose escalation part, if fulfilling the inclusion criteria of the expansion part and if the planned dose and dosing schedule are the same as in dose expansion will be included in the analyses of dose expansion. Note (not needed to be specified in the SAP) in case this approach is selected: to clearly see how many participants from dose escalation contribute to the results of the dose expansion, the analysis populations table for the analysis of the expansion part will include 3 columns: one for participants coming from dose escalation, one for participants coming from dose expansion, one All (other columns will be needed to separate arms using different regimen, if several regimen are investigated). All the other tables of the expansion part with only include the column All.
* For studies with multiple tumor types/indications and/or doses/regimen. Safety data will be summarized by tumor type/indication, dose/regimen, and then can be combined at same dose/regimen across tumor types/indications. Efficacy data will always be analyzed by tumor type/indication and dose/regimen and never be combined. In dose expansion part, unless otherwise specified, analyses will be performed by [tumor type/indication], by dose level and overall (except for efficacy and PDy analyses). In addition, safety analyses will be presented by dose level across [tumor types/indications]. Unless otherwise specified, analyses will be based on the intended dose level at C1D1. Participants included in the dose escalation part, if fulfilling the inclusion criteria of the expansion part and if the planned dose and dosing schedule are the same as in dose expansion will be included in the analyses of dose expansion. Same instruction as for previous bullet.

<End of example text for early phase oncology studies with dose escalation and dose expansion parts >

***Observation period***

Please adapt the observation period definitions for study with multiple-period designs. Please select one of the following 2 options depending on the study.

<Option 1: studies with ‘treatment-emergent period’ different than ‘on-treatment period’. Mostly apply to non-oncology studies>

<Start of common text>

The observation period will be divided into 4 segments:

* The **pre-treatment period** is defined as the period up to first investigational medicinal product (IMP) administration.
* The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + Y days. (Y is determined by the profile of the experimental product (eg, 5 elimination half-lives) and generally will be the same for all studies within a project as defined in the clinical trial protocol) The treatment-emergent period includes the following 2 periods:
* The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + X days (X is the planned time between 2 administrations (eg, +1 day if daily administrations, +7 days for Q1W administrations)
* The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
* The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

<End of common text>

<Option 2: studies with ‘treatment-emergent period’ same as ‘on-treatment period’. Mostly apply to oncology studies>

<Start of common text>

The observation period will be divided into 3 segments:

* The **pre-treatment period** is defined as the period up to first IMP administration.
* The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration + X days. (X is determined by the profile of the experimental product (eg, 30 days can be used for oncology studies) and generally will be the same for all studies within a project as defined in the clinical trial protocol)
* The **post-treatment period** is defined as the period from the end of the on-treatment period.

<End of common text>

On-study period is optional, to be defined if needed for analysis or requested by health authorities.

<Start of suggested text – generally not applicable for oncology>

The on-study period is defined as the time from [randomization/enrollment/first IMP] until the end of the study defined as the last scheduled visit for those who completed the study and the end-of-study date collected on electronic case report form (e-CRF) page “Completion of End of Study” for those who did not complete the study. If death is the end-of-study reason, date of death will be used.

<End of suggested text>

## Primary endpoint(s) analysis

This section intends to capture primary endpoint definition and analytical approaches, regardless of whether it is an efficacy endpoint or another type of endpoint (eg, safety, PK). The information will be copied from the protocol. Additional details may be added, including analysis related to COVID-19 impact, such as missing data handling, etc, if applicable.

If non-efficacy endpoints are included in list of primary endpoints in protocol, instead of describing details in primary endpoint analysis section, suggest referencing the analysis of those endpoints to the corresponding sections (eg, [Section](#_Ref43156537) 3.6.2 for AEs, [Section](#_Ref84227982) 3.6.3.1 for lab/vital signs/ECG, [Section](#_Ref43156570) 3.7.1.1 for PK, etc.). Sub-sections of [Section](#_Ref84228050) 3.2 may be removed. However, in case one of these endpoints is part of the hypothesis testing and/or is analyzed with a statistical model (eg, MACE safety endpoint in diabetes studies), full details of this endpoint and its analysis should be described under this Section.

<Start of example text>

<Start of example text for studies with non-efficacy endpoints as primary endpoints>

The primary endpoints detailed in this section are XXX. Other primary endpoints analyses are defined in [Section](#_Ref43156537) 3.6.2 (AE, SAE), [Section](#_Ref84228134) 3.6.3.1 (laboratory abnormalities), [Section](#_Ref43156570) 3.7.1.1 (PK) and [Section](#_Ref121388538) 3.7.1.2 (immunogenicity).

<End of example text>

<Start of example text for early phase oncology studies with safety as primary endpoint for dose escalation and efficacy (ORR) as primary endpoint for dose expansion >

The primary endpoint detailed in this section is ORR (for expansion part). Primary endpoint of escalation part is defined in [Section](#_Ref43156537) 3.6.2 (AE, SAE).

<End of example text for early phase oncology studies >

### Definition of endpoint(s)

In this section,

* State how the primary endpoint(s) will be defined/calculated/derived
* Describe if the endpoint will be transformed, such as square-root and logarithm, before analysis. It is recommended including rationale/justification for transformation and the interpretation

The definition of the primary endpoint should be taken directly from the primary endpoint definition in the final protocol, including amendments. Additional details can be added here to help a reviewer perform the primary analysis based on SAP, for example, specify analysis windows if used to define the endpoint. If analysis windows are used beyond primary endpoint (eg, for secondary endpoints and/or safety endpoints), it is recommended defining these analysis windows in Appendix 4 Data Handling Conventions. In case multiple imputation is used, state imputation model, number of datasets, and seed. Specify how analysis results derived from individual imputed datasets will be combined.

<Start of example>

The primary endpoint is the absolute change from baseline to week 26 in HbA1c. All the efficacy assessments collected during the study will be used, including those obtained after IMP discontinuation or introduction of rescue therapy.

<End of example>

### Main analytical approach

The specification of the primary analysis should be taken directly from the final protocol, including amendments.

* Specify the estimand attributes, refer to estimand(s) in [Section](#_Ref43159550) 1.2.1 and ICH E9 (R1), if applicable:
  + the treatment condition (ie, which treatment groups will be compared) and the statistical hypothesis
  + the analysis population
  + how anticipated intercurrent events (eg, intervention discontinuation) will be handled and how collected data after intercurrent events will be considered in the analysis.
  + the main analytical approach(es) (aligned to the primary estimand(s)) and the underlying assumption of the main analytical approach(es), the assumptions and how missing data will be handled. If imputation methods differ across different intercurrent events, describe how. In case of multiple imputation, state imputation model, number of data sets and seed. Specify how analysis results derived from individual imputed data sets will be combined.
* Describe (if applicable) factors, covariates, stratification factors etc to be included in the analysis model. In case of more than two intervention groups, define which intervention contrasts will be provided. Describe model assumption diagnostics, if relevant.
* Describe how analysis results will be presented such as estimated treatment difference, 95% confidence intervals (90% CI may be preferred for early phase oncology studies, excepted in case of potential accelerated approval), p-values, forest plots etc Recommended to describe how the endpoint(s) will be summarized descriptively.
* For event-driven studies, suggest specifying the summary of participant status at the common study end date (CSED). For example, for a study with MACE as primary endpoint, the status at CSED could include information such as if participant alive or death at CSED; if had primary endpoint event or not, if was followed-up for CV events up to CSED/death etc For participants with CV events follow-up discontinued before CSED/death, the time from discontinuation to CSED/death may be summarized.
* Suggest providing sample program code for the analysis model, in appendix, if it is complicated.

< Start example text 1 for Estimands >

The primary endpoint will be analyzed with the Estimand 1 defined according to the following attributes:

* Endpoint: Change from baseline in clinical variable to timepoint
* Treatment condition: Compound number will be compared to XXX, on top of background therapy.
* Analysis population: ITT population
* Intercurrent events (IE):
* The IMP discontinuation IE will be handled with the treatment policy strategy; The primary endpoint will be assessed based on all assessments irrespective of the IMP discontinuation
* The rescue medication IE will be handled with the hypothetical strategy; The primary endpoint will be assessed based on assessments up to the initiation of rescue medication
* …
* Population-level summary: Mean difference between interventions from analysis of covariance (ANCOVA) with XXX as fixed effects. Missing data imputed with multiple imputation using post-treatment data of participants from same randomized arm.

< End of example text 1 for Estimands >

< Start example text 2 for Estimands >

The primary endpoint will be analyzed with the main estimand as defined in Table 8.

Table 8 - Primary endpoint: Main estimand

| Main estimand attributes | |
| --- | --- |
| Endpoint | Change from baseline in clinical variable *to* timepoint |
| Treatment condition | Compound number *versus* XXX |
| Analysis population | ITT |
| Intercurrent events | Had rescue medication not been administered (hypothetical strategy) and regardless of study treatment discontinuation due to an AE (treatment policy strategy) |
| Population-level summary | Mean difference between treatment groups from analysis of covariance (ANCOVA) with XXX as fixed effects. Missing data imputed with multiple imputation using post-treatment data of participants from same randomized arm |

< End of example text 2 for Estimands >

### Sensitivity analysis

Sensitivity analyses are a series of analyses targeting the same estimand as the primary estimand, with differing assumptions to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

Describe the planned sensitivity analyses and how the sensitivity analyses will target the assumptions behind the main analytical approach(es). Pay special attention to assumptions regarding the missing data mechanism.

Enter Primary Sensitivity Analyses

### Supplementary analyses

Supplementary analyses are a general description for analyses that are conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect. The term describes a broader class of analyses than sensitivity analyses. Each supplementary analysis may refer to a different estimand than the primary estimand. Where the primary estimand(s) of interest is agreed between sponsor and regulator, and the main estimator is pre-specified unambiguously, supplementary analyses should generally be given lower priority than a sensitivity analysis.

Enter Primary Supplementary Analyses

## Secondary endpoint(s) analysis

For endpoints analyzed using the same methodology as the primary efficacy analysis, suggest cross-referencing the primary efficacy analysis.

If non-efficacy endpoints are included in list of secondary endpoints in protocol, instead of describing details in secondary endpoints analysis section, suggest referencing the analysis of those endpoints to the corresponding sections (eg, [Section](#_Ref43156537) 3.6.2 for AEs, [Section](#_Ref84228335) 3.6.3.1 for lab/vital signs/ECG, [Section](#_Ref43156570) 3.7.1.1 for PK, etc). However, in case one of these endpoints is part of the hypothesis testing and/or is analyzed with a statistical model (eg, MACE safety endpoint in diabetes studies), full details of this endpoint and its analysis should be described under this Section.

<Start of example text>

The secondary endpoints detailed in this section are XXX. Other secondary endpoints analyses are defined in [Section](#_Ref43156537) 3.6.2 (AE, SAE), [Section](#_Ref84228434) 3.6.3.1 (laboratory abnormalities), [Section](#_Ref43156570) 3.7.1.1 (PK) and [Section](#_Ref121388747) 3.7.1.2 (immunogenicity).

<End of example text>

<Start of example text for early phase oncology studies with safety as primary endpoint for dose escalation and efficacy (ORR) as primary endpoint for dose expansion >

The secondary endpoints detailed in this section are secondary efficacy endpoints: DoR and PFS. The ORR analyses of the escalation part will follow similar approach as described in [Section](#_Ref84228524) 3.2 (primary endpoint of the expansion part) and therefore will not be described below. Other secondary endpoints analyses are defined in [Section](#_Ref43156537) 3.6.2 (AE, SAE), [Section](#_Ref84228578) 3.6.3.1 (laboratory abnormalities), [Section](#_Ref43156570) 3.7.1.1 (PK) and [Section](#_Ref121388941) 3.7.1.2 (immunogenicity).

<End of example text for early phase oncology studies >

### Key/Confirmatory secondary endpoint(s)

Similar instructions as for primary endpoint sections. Key secondary endpoints are those for indication claim or key label endpoints and are part of the confirmatory hypotheses with Type I error control. They should be described at the same level of details as the primary endpoint(s) Section.

Enter Key Secondary Endpoints

#### Definition of endpoint(s)

Enter Key Definition of Endpoints

#### Main analytical approach

Enter Key Main Analytical Approach

#### Sensitivity analysis

Sensitivity analysis will generally not be performed for secondary endpoints unless requested by agency. Remove this section if no sensitivity analysis for secondary endpoints.

Enter Key Sensitivity Anlyses

#### Supplementary analysis

Supportive analysis will generally not be performed for secondary endpoints unless requested by agency. Remove this section if no supportive analysis for secondary endpoints.

Enter Key Supplementary Analyses

### Supportive secondary endpoint(s)

Similar instructions as for primary and key secondary endpoint sections. For endpoints analyzed using the same methodology as the primary or key secondary endpoints, cross-reference the primary or key secondary endpoints analysis.

Enter Supportive Secondary Endpoints

## Tertiary/exploratory endpoint(s) analysis

Similar instructions as for primary and secondary endpoint sections. For endpoints analyzed using the same methodology as the primary or secondary endpoints analysis, cross-reference the primary or secondary endpoints analysis. A reference to the subsequent sections can be made, if applicable.

<Start of example text>

The tertiary endpoints detailed in this section are XXX. Other tertiary endpoints analyses are defined in [Section](#_Ref43156537) 3.6.2 (AE, SAE), [Section](#_Ref84228705) 3.6.3.1 (laboratory abnormalities), [Section](#_Ref43156570) 3.7.1.1 (PK) and [Section](#_Ref121486752) 3.7.1.2 (immunogenicity).

<End of example text>

### Definition of endpoint(s)

Enter Tertiary/Exploratory Definition of Endpoints

### Main analytical approach

Enter Tertiary/Exploratory Main Analytical Approach

## Multiplicity issues

This information will generally be copied directly from the Multiplicity Adjustment section of the protocol. Additional details may be added.

Provide an overview of the adjustments for multiplicity with respect to the analysis of primary and key secondary endpoints along with the technical details. If there is no issue with multiplicity, that needs to be stated.

Enter Multiplicity Issues

## Other safety analyses

“Other” to be kept in the section title only if safety endpoint(s) are part of endpoints described in [Section](#_Ref84228810) 3.2 , [Section](#_Ref84228831) 3.2.3 and [Section](#_Ref84228854) 3.4.

In this template, safety analyses focus on on-treatment and/or treatment-emergent periods. If requested by health authorities or if relevant for the product, on-study analyses may be conducted for benefit-risk purposes.

The primary focus of AE reporting will be on TEAEs. Information on this section will be copied from protocol Section 9.4.5 “Other Safety Analysis”. If needed, it can be edited, and additional details may be added.

At time of interpretation of safety results, special care will need to be made about potential for bias in case pattern of treatment discontinuations (reason, treatment duration, initiation of rescue therapy) is different between treatment groups.

<Start of common text>

All safety analyses will be performed on the [safety/exposed] population as defined in [Section](#_Ref120775781) 2, unless otherwise specified, using the following common rules:

* The analysis of the safety variables will be essentially descriptive, and no testing is planned.
* Safety data in participants who do not belong to the [safety/exposed] population (eg, exposed but not [enrolled/randomized]) will be provided.

<End of common text>

### Extent of exposure

Participant exposure to IMP, compliance calculations (if relevant) and summaries can be defined briefly in this section. Please adapt the text for multiple period study design, or to account for oral agents, infusions, injections, or other non-oral administrations. For studies with interim analysis, exposure calculations for interim analysis can be specified in Section 4.9 Interim Analysis.

<Start of suggested text for non-oncology>

sub-sections [Section](#_Ref43156666) 3.6.1.1 and [Section](#_Ref43156678) 3.6.1.2 are only applicable to oncology

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized [within the safety/exposed population]. In addition, summaries will be provided [by trial impact (disruption) due to COVID-19/in the population with trial impact (disruption) due to COVID-19].

**Duration of IMP exposure**

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + Y days, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing (Y is the planned time between 2 administrations, eg, +1 day if daily administrations, +7 days for Q1W administrations).

Duration of IMP exposure will be summarized quantitatively and categorically: 1 to 7, 8 to 14, 15 to 21, 22 to 28, and >28 days. The categories and unit will be adapted to the study. In case of dose titration, a description might be provided by period or by dose.

Additionally, the cumulative duration of treatment exposure (expressed in participant-[years/months]) will be provided.

<End of suggested text for non-oncology>

In general, it is recommended not to derive complicated treatment compliance and avoid intensive missing data imputation for treatment compliance calculation. The CRF should be designed to allow identification of the administrations considered as non-compliant to avoid missing or incomplete data imputation.

<Start of suggested text for non-oncology, only if compliance is needed>

**Treatment compliance**

A given administration will be considered noncompliant if the participant did not receive the number of administration/days as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of [administrations/days] that the participant was compliant divided by the total number of [administrations/days] that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

If the comparator is not administered at the same time as the IMP and if there is a double-dummy placebo, then separate compliance indicators may be defined.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

<End of suggested text>

<Start of suggested text for oncology>

Text is provided for a treatment scenario consisting of a combo of two drugs, ie, DRUG1 and DRUG2. The summary of exposure is divided into three parts: Overall exposure, DRUG1 exposure and DRUG2 exposure. In the case of monotherapy (ie, DRUG1 only), modify the text to exclude references to DRUG2 and remove subsections. Please adapt the wording for the studies where cycle concept not applicable.

If applicable, summaries will be provided [by trial impact (disruption) due to COVID-19/in the population with trial impact (disruption) due to COVID-19].

#### Overall exposure

The dose information will be assessed by the following variables:

* Overall number of cycles started, defined by the number of cycles in which at least one dose of any study interventions is administered.
* Duration of IMP exposure (in weeks) is defined as (Last day of exposure – first day of exposure +1)/7.
* The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP (DRUG1, DRUG2).

The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:

* The last administration date + the number of theoretical days until the next administration -1 for DRUG1,
* The last administration date + the number of theoretical days until the next administration -1 for DRUG2.

The total number of cycles started, number of cycles started by participants will be summarized as a quantitative variable and by category (number (%) of participants receiving at least 1 cycle, at least 2 cycles, etc). Optional and could be adapted to for example 1-4 cycles, 5-8 cycles depending of the cycle duration. Could be adapted also with number of infusions. The duration of overall exposure will be summarized quantitatively.

The following variable will be computed to describe overall dose modification (cycle delay):

Make sure the definition is consistent with cycle delay defined in protocol.

* Cycle delay: A cycle is deemed as delayed if the start date of the current cycle – theoretical duration of a cycle – start date of the previous cycle is > xx days. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the participant (with number of participants used as denominator) and cycle (with number of cycles used as denominator) levels, as follows:

A participant exposed during a long time has a higher chance of a cycle delay than a participant exposed shorter. However, all treated population is recommended for simplicity, since the by-participant analysis will introduce bias regardless of selected population. Additional analyses may be added in the SAP using a different participant population, such as all participants treated with at least 2 cycles started, or time(cycle)-to-event analysis.

* Number (%) of participants with a least 1 cycle delayed
* Number (%) of participants with a cycle delayed between xx and 7 days (using maximum delay across all cycles)
* Number (%) of participants with a cycle delayed >7 days (using maximum delay across all cycles)
* Number (%) of cycles delayed
* Number (%) of cycles delayed between xx and 7 days
* Number (%) of cycles delayed >7 days

#### DRUG1 exposure

Dose is used in this section but can be replaced by another wording (cycle, infusion, injection etc) corresponding to the drug profile. The units, indicated in mg in the text below, can also be adapted if dose is measured in different units, such as mg/kg.

The dose information will be assessed by the following:

* Total number of cycles started
* Number of cycles started per participant. The first bullet refers to the total number of cycles across participants, while the second bullet refers to the number of cycles for each participant.
* Duration of DRUG1 exposure (in weeks) is defined by date of last administration of DRUG1 + number of theoretical days until the next administration – date of first administration of DRUG1/7.
* Actual dose (mg)
* Cumulative dose (mg): the cumulative dose is the sum of all actual doses of DRUG1, given from first to last administration
* Actual dose intensity (ADI in mg/week): defined as the cumulative dose divided by the duration of DRUG1 exposure (in weeks)
* Planned dose intensity (PDI in mg/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 4 weeks per cycle started)
* Relative dose intensity (RDI, in %)
* The total number of doses, total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc) Optional and could be adapted to 1-4 cycles, 5-8 cycles depending of the cycle duration. Duration of DRUG1 exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

* Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent DRUG1 administrations, dose reduction will be determined using the dose level intervals provided in Table 9, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

The dose levels and intervals should be defined according to dose reduction steps provided in the protocol. If the defined dose reduction steps are original dose at 20 mg, 1st dose reduction at 10 mg, 2nd dose reduction at 5 mg, then the dose levels and intervals can be found in the following table.

Table 9 - DRUG1 dose reduction criteria

| Actual dose level | Dose level interval |
| --- | --- |
| Starting dose (20 mg) | >15 mg |
| Dose level -1 (10 mg) | >7.5 mg and ≤15 mg |
| Dose level -2 (5 mg) | >2.5 mg/kg and ≤7.5 mg |
| Dose level -3 (low dose) | >0 mg and ≤2.5 mg |

* Dose omission is defined as a dose not administered at the scheduled visit. “Not taken” information from eCRF dosing page to be taken into account to identify dose omissions.
* Dose delay is defined as to be completed includes dose delays at CxD1 and at any other administrations of the cycle. Dose delay does not apply to studies with daily administrations without rest period.
* Dose interruption: A dose will be considered to be interrupted if the DRUG1 administration is stopped during an infusion regardless of whether it is restarted or not Optional. Depending on the collection method, it is possible to classify dose interruption into two categories: 1) dose interrupted and restarted, 2) dose interrupted and not restarted. This information will come directly from the eCRF and should not be derived.

Dose modifications and dose interruptions will be analyzed by participant, cycle and dose as follows:

* **Participant** (number of participants treated will be used as denominator)
* Number (%) of participants with at least 1 dose modification
  + Number (%) of participants with at least 1 dose delayed
  + Number (%) of participants with at least 1 dose reduction
  + Number (%) of participants with at least 1 dose omission
* Number (%) of participants with a least 1 dose interruption
  + Number (%) of participants with at least 1 dose interruption restarted
  + Number (%) of participants with at least 1 dose interruption definitively stopped
* **Cycle** (number of cycles started will be used as denominator)
* Number (%) of cycles with at least 1 dose modification
  + Number (%) of cycles with at least 1 dose delayed
  + Number (%) of cycles with at least 1 dose reduction
  + Number (%) of cycles with at least 1 dose omission
* Number (%) of cycles with at least 1 dose interruption
  + Number (%) of cycles with at least 1 dose interruption restarted
  + Number (%) of cycles with at least 1 dose interruption definitively stopped
* **Dose** (number of doses started will be used as denominator) Depending on the administrations schedule, analysis by dose could be more appropriate than analysis by cycle
* Number (%) of dose interruptions
* Number (%) of dose reductions (including dose omissions)

#### DRUG2 exposure

Use similar text as for DRUG1 as appropriate

<End of suggested text for oncology>

### Adverse events

A large set of possible analyses are provided in this section. Make a selection considering the study size, the study phase, the duration of the treatment, the number of studies in the program (for example, in case several studies can be pooled together/meta-analysis can be performed, the safety analyses may be extensive in the pool (described in a separate SAP) and less extensive at study level).

**General common rules for adverse events**

<Start of common text>

For studies not using CTCAE (National cancer institute common terminology for adverse events)

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version [currently in effect at Sanofi at the time of database lock/X.X]. Specify MedDRA version if known and fixed due to project specifics

For studies using CTCAE

All AEs will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE version X.X) and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version [currently in effect at Sanofi at the time of database lock/X.X]. Specify MedDRA version if known and fixed due to project specifics

For all studies

The AEs will be analyzed in the following 3 categories:

* Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
* Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
* Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing [severity/grade] will be left as missing.

For studies not using CTCAE

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

For studies using CTCAE

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for grade ≥3 (including grade 5). Missing grades, if any, will be included in the “all grades” category.

For all studies

The AE tables will be sorted as indicated in Table 10. Not all presentations have to be selected, make a selection (for example, the presentation by SOC and PT may be sufficient for analyses of individual studies while presentation by 4 or 3 MedDRA levels, if not mandatory for individual studies in the QSD-002873 (standard outputs), may only be used at pool/meta-analysis level)

Table 10 - Sorting of AE tables

| AE presentation | Sorting rules |
| --- | --- |
| SOC, HLGT, HLT and PT | By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs. |
| SOC, HLT and PT | By the internationally agreed SOC order and by alphabetic order of HLTs and PTs. |
| SOC and PT | By the internationally agreed SOC order and decreasing frequency of PTsa,b |
| [SMQ/CMQ] and PT | By decreasing frequency of [SMQs/CMQs] and PTsa |
| PT | By decreasing frequency of PTsa |
| 1. Sorting will be based on the [Compound number intervention group/Compound number xx mg dose intervention group/overall incidence] Sorting will be based on the experimental study intervention group. For studies with multiple intervention groups, sorting will be based on the experimental arm with the highest dose/severity. For single-arm studies, sorting will be based on the overall incidence. 2. The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified. | |

<End of common text>

For all studies unless otherwise specified

**Analysis of all adverse events**

No guidance is provided in this template regarding which analyses are mandatory vs. optional. Refer to QSD-002873 (standard outputs) for the list of mandatory outputs. Generally, the number of summaries is to be decided based on the study size, the number of studies in the program (eg, in case several studies can be pooled together/meta-analysis can be performed, the safety analyses may be extensive in the pool (described in a separate SAP) and less extensive at studies level). For example, if not mandatory for individual studies in the QSD-002873 (standard outputs), replacement of 4-MedDRA level tables by 3-MedDRA level tables (SOC, HLT, PT) may be considered.

Analyses by Grade are applicable for studies using CTCAE (Common Terminology Criteria for Adverse Events) criteria (eg, oncology studies).

<Start of common text>

The overview of TEAE with the details below will be generated:

* Any TEAE
* Any grade ≥3 TEAE for studies using CTCAE
* Any treatment-emergent SAE
* TEAE leading to death for non-oncology studies only
* Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period) Participants experiencing a TEAE with any grade except Grade 5 during the treatment emergent-period and who die due to the AE in the post-treatment period will not be considered as Grade 5 TEAE but as a post-treatment Grade 5 AE.
* Any TEAE leading to permanent intervention discontinuation for monotherapy studies
* Any TEAE leading to permanent full intervention discontinuation for combination studies (ie, studies with a combination intervention). When all interventions are not discontinued at the same time, the reason for permanent full discontinuation is the reason for discontinuation of the last intervention(s) stopped
* Any TEAE leading to permanent partial intervention discontinuation (discontinuation of Compound number) applicable to combination studies where some interventions of the combo can be continued while other(s) are discontinued. In such case, include at least the analysis of TEAE leading to the discontinuation of the intervention of interest.

The AE summaries of Table 11 will be generated with number (%) of participants experiencing at least one event. For studies using CTCAE: The analyses will be performed for all grades combined and for grades ≥3. The all TEAE summary by Primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 11 - Analyses of adverse events

| Type of AE | MedDRA levels |
| --- | --- |
| All TEAE | Primary SOC, [HGLT, HLT/HLT] and PT |
|  | Primary SOC and PT |
|  | Primary SOC |
|  | PT |
|  | Primary and secondary SOC, [HGLT, HLT/HLT] and PT |
| Common TEAE (≥X% in [Compound number/any group]) | Primary SOC and PT |
| TEAE related to [IMP/intervention x] as per Investigator’s judgment | Primary SOC, [HGLT, HLT/HLT] and PT |
|  | Primary SOC and PT |
| TEAE by maximal intensity | Primary SOC and PT for non-oncology |
| Treatment emergent SAE | Primary SOC, [HGLT, HLT/HLT] and PT |
|  | Primary SOC and PT |
| Treatment emergent SAE related to [IMP/intervention x] as per Investigator’s judgment | Primary SOC, [HGLT, HLT/HLT] and PT |
| TEAE leading to permanent full intervention discontinuation | Primary SOC, [HGLT, HLT/HLT] and PT |
|  | Primary SOC and PT |
| TEAE leading to permanent partial intervention discontinuation (discontinuation of intervention x) | Primary SOC, [HGLT, HLT/HLT] and PT |
|  | Primary SOC and PT |
| TEAE leading to deathb | Primary SOC, [HGLT, HLT/HLT] and PT |
| AE leading to deathb  - In context of disease progressionc  - In context other than disease progressiond | Primary SOC and PT for oncology |
|  | Primary SOC and PT |
| Pretreatment AE | Overviewa |
|  | Primary SOC and PT |
| Post-treatment AE | Overviewa |
|  | Primary SOC and PT |
| Post-treatment SAE | Primary SOC and PT |
| TEAE leading to dose modification (including dose delay, dose reduction and dose omission) | Primary SOC and PT for oncology |
| TEAE leading to dose interruption | Primary SOC and PT for oncology |
| 1. Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent full intervention discontinuation 2. Death as an outcome of the AE as reported by the Investigator in the AE page 3. Death within 30 days from last IMP administration and the cause of death is disease progression 4. Death within 30 days from last IMP administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last IMP administration and the cause of death is AE | |

<End of suggested text>

For large studies not planned to be pooled with other studies, consider including relative risks, hazard ratios or absolute differences for TEAEs experienced by at least n participants overall in the safety/exposed population. This threshold may be defined as the minimum number of participants with the event (n) observed overall (regardless of the intervention group) needed so that the extreme case scenario (n for SARxxxxxx versus 0 for the control group) leads to a 95% CI excluding 1 (for relative difference) or 0 (for absolute difference) for the comparison of the 2 intervention groups.

If any clinically significant signal is detected and need further characterization, additional analyses similar to analyses done for AESIs can be provided.

**Analysis of deaths**

<Start of common text>

In addition to the analyses of deaths included in Table 10 the number (%) of participants in the following categories will be provided:

* Deaths during the treatment-emergent and post-treatment periods by main reason for death if collected in the death eCRF form. If needed, deaths can be summarized as on-study vs. post-study
* For studies using CTCAE: An overview of Grade 5 AEs will be provided with the following categories:
* Grade 5 AE (TEAE and post-treatment).
* Fatal TEAE (regardless of date of death/period).
  + Grade 5 TEAE with a fatal outcome during the treatment-emergent period,
  + Any Grade TEAE with a fatal outcome during the post-treatment period.
* Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).
* Deaths in [non-randomized/non-enrolled] participants or [enrolled/randomized] but not treated participants

<End of common text>

**Analysis of adverse events of special interest (AESIs)** **and other AEs of interest**

Provide how the AESIs (and other AEs of interest if appropriate) will be selected for the analyses, including standardized MedDRA queries (SMQ) and Company MedDRA queries (CMQ). For early phase oncology studies, dose-limiting toxicities (and AEs post DLT observation period meeting DLT criteria, if relevant) will generally be included here as a specific event of interest, even if overlaps exist with other events of interest. Some examples of selection are provided in the table. In case a CMQ is used, the list of terms should come from the coding department and analysis to be programmed using CMQ instead of based on individual terms. CMQ name should be specified in the SAP together with the list of terms with MedDRA version (in appendix if too long for the table) and the following footnote should be included “The list of terms may be adjusted according to MedDRA version changes”. The adjustment of the list of terms will be documented in the CSR (SAP amendment not needed).

<Start of suggested text>

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 12. Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 10.

Table 12 - Selections for AESIs and other AEs of interest

| AESIs and other AEs of interest | Selection |
| --- | --- |
| XX | e-CRF specific tick box on the AE page |
| XX | SMQ XX [“broad and narrow”/”narrow”] |
| XX | CMQ name based on the following HLTs XX and PTs XXa |
| DLT for early phase oncology studies | e-CRF specific DLT page |
| AE meeting DLT criteria beyond DLT observation period for early phase oncology studies | e-CRF specific page |
| AE related to COVID-19 illness | selection to be specified |
| 1. The list of terms may be adjusted according to MedDRA version changes | |

The following analyses can be added for dose escalation studies driven by BLRM

For DLT analysis, the following will be provided:

* Posterior probability of DLT rate within the target range (16% to 33%)
* Posterior probability of DLT rate above the target range (>33%)
* Median and 95% CI of DLT rate posterior distribution

The following bayesian logistic regression model will be used to derive these statistics:

logit(pi) = log[a] + exp (log[b]) log (di/dref)

where pi is the probability of DLT for a participant at dose level di, a and b are parameters that are random variables, and dref is the reference dose (xx µg/kg).

A bivariate normal joint distribution will be used for the prior with the following 5 parameters: μa= x.xxxx, σa= x.xxxx, μb= x.xxxx, σb= x.xxxx, ρ=0. In case these parameters are modified compared to the protocol, specify why (eg, emerging data from outside of this study).

The analyses below are optional. They are provided as examples of analyses to further characterize a safety signal. Select the appropriate analyses according to the study size, treatment duration and the number of studies in the program (for example, in case several studies can be pooled together, the safety analyses may be extensive in the pool (described in a separate SAP) and less extensive at study level). Recurrent events analysis may also be performed.

Relative risk, odds-ratio or absolute difference may be preferred to hazard ratio depending on the treatment duration. In such case, Cox model and Kaplan-Meier curves needs to be replaced (for example by logistic regression model for odds-ratio)

* 95% CI of the incidence rate will be provided using [mid-p/Clopper-Pearson] method.
* Event rate per participant-years (number of participants with an event in question divided by total participant-years) and 95% CI will be provided. For participants with an event, the number of participant-years will be censored at time of the first event; for participants without an event, the number of participant-years corresponds to the length of the treatment-emergent period.
* In order to compare treatment groups, the [hazard ratio (HR)] and 95% CI will be provided [for time from first dose of treatment to the first occurrence of the event using a Cox proportional hazards model]. [Kaplan-Meier curves will be provided. Participants without any event will be censored at the end of the treatment-emergent period.]
* To assess the homogeneity of the treatment effect across subgroups: Number (%) of participants experiencing at least one event will be provided by [XXX]
* Overview summary with number (%) of participants with TEAE, Serious TEAE, TEAE leading to death and TEAE leading to permanent discontinuation of intervention
* Summary of the following characteristics will be provided: the number of episodes, the mean duration of the event, the intensity (mild, moderate, severe), the outcome (Recovered/Resolved, Recovering/Resolving, Unknown, Recovered/Resolved with sequelae, Stabilized, Not recovered/Not Resolved, Fatal), the seriousness (Yes, No), the use of corrective treatment (Yes, No).

<End of suggested text>

### Additional safety assessments

#### Laboratory variables, vital signs and electrocardiograms (ECGs)

All laboratory data, vital signs and ECG presentations will be generated using the Guideline for the Analysis and Reporting of Safety Data from Clinical Trials (BTD-009536).

In this section, provide:

* The list of laboratory variables, vital signs and ECG variables that will be analyzed. (exclude parameters only collected at baseline or parameters only collected in case a specific AE occurs, the full list being provided in the protocol)
* If applicable, how the quantitative analyses will be performed
* How the analyses according to PCSA and NCI (for studies using CTCAE) will be conducted

In this section, analyses details are jointly provided for laboratory variables, vital signs and ECG variables to avoid redundancy.

The PCSA criteria currently in effect at Sanofi at the time of the database lock should be listed in CSR appendices.

<Start of common text>

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units and conventional unit, if applicable.

* Hematology:
* Red blood cells and platelets and coagulation: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, red blood cell count, platelet count, prothrombin time (expressed as international normalized ratio), activated partial thromboplastin time, sedimentation rate
* White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
* Clinical chemistry:
* Metabolism: glucose, HbA1c, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, total protein, albumin, creatine phosphokinase, lipase, amylase, C-reactive protein
* Electrolytes: sodium, potassium, chloride, calcium/calcium corrected/ionized calcium, phosphorus, bicarbonate, magnesium Calcium is to be selected for studies not using CTCAE. Corrected calcium (if ionized calcium is not collected) or ionized calcium is to be selected for studies using CTCAE. If total calcium is collected then corrected calcium will be derived from total calcium (in such case, include the formulae below in the SAP). If corrected calcium is directly collected, it will directly be used in the analyses. It should be avoided summarizing a mix of corrected calcium results from investigator and corrected calcium derived from total calcium.

Calcium Corrected (mmol/L) = Total calcium (mmol/L) + 0.8 \* 0.25 \* [4 – Serum albumin (g/L) \* 0.1]

* Renal function: creatinine, eGFR, creatinine clearance, blood urea nitrogen, urea, uric acid. Creatinine clearance will be derived with the equation of Cockcroft and Gault using weight assessed at the same visit as creatinine. eGFR will be derived using the Modification of the Diet in Renal Disease (MDRD) equation: formulae to be included. This sentence about the derivation and formulae are to be removed if creatinine clearance is directly collected in the eCRF (ie, derivation performed by the sites).
* Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, total and direct bilirubin
* Pregnancy test: Serum β-human chorionic gonadotropin (all female participants)
* Hepatitis screen: hepatitis B surface antigen, anti-hepatitis-C antibody
* Urinalysis:
* Urinalysis for quantitative analysis: pH, specific gravity, proteins, and glucose
* Urine electrolytes: sodium, potassium, creatinine, and osmolality assessed from freshly voided morning urine collection
* Vital signs: heart rate, systolic and diastolic blood pressure according to position (sitting, standing, supine), orthostatic changes in blood pressure, weight, respiratory rate, temperature, ECOG Performance status and/or body surface area
* ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia)/ECG assessments will be described as normal or abnormal The Fridericia formula is recommended in the guideline for the Analysis and Reporting of Safety Data from Clinical Trials (BTD-009536). For drugs known to potentially alter heart rate, consider also including QTcB.

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Appendix xx). For other biochemistry parameters, grading will be derived using local laboratory normal ranges.

Appendix to be added in [Section](#_Ref84228988) 5 if applicable. Use of sanofi generic ranges is not recommended when a central lab is used or when local normal ranges can be retrieved

**Quantitative analyses**

When relevant, for laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for [each planned visit/each analysis window], the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using [central measurements only (when available), local measurements] for laboratory variables and ECG variables.

Quantitative analyses are recommended for example for chronic non-life-threatening diseases.

Depending on the study, planned visits will be displayed (considering only planned assessments) or re-allocated visits (defined by analysis windows considering actual sample dates and unscheduled assessments).

It is preferred to perform quantitative analyses only for studies using central laboratory. Nevertheless, if local laboratories have to be used, it is to be considered whether the analysis should be performed with or without normalization of data depending on the laboratory measurement.

Quantitative analyses may not apply for dose-escalation parts/studies.

For parameter 1, …, parameter n, mean changes from baseline with the corresponding standard error will be plotted over time. Boxplot may be produced instead of line plot if needed

**Analyses according to PCSA and NCI grading**

<Start of common text>

For studies not using CTCAE

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable For parameters without PCSA criterion, it is recommended that a relevant threshold is determined by the clinical team, if possible. If not possible, the relevance of an analysis using normal range should be discussed. For parameters defined as efficacy endpoints, PCSA summaries will not be provided.

For studies using CTCAE

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version X.X). In addition, for [parameter1,…, parameter n/laboratory variables for which NCI-CTCAE scale is not applicable], vital signs and ECG variables, PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

If needed, the predefined list of PCSA criteria can be adapted for a study/compound. These adaptations should be described in the SAP.

For all studies

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

* Normal/missing
* Abnormal according to PCSA criterion or criteria

For studies using CTCAE

For laboratory variables graded by NCI-CTCAE,

* The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
* The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided. Add specific statement to assess toxicity for parameters not graded according to NCI if applicable

The following analysis will be conducted if normal/abnormal result is retrieved but quantitative results of ECG variables (eg, heart rate, PR, QRS…) are not retrieved.

<Start of suggested text>

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

* Normal/missing
* Abnormal

<End of suggested text>

For selected interventions, including those with potential for liver injury:

<Start of suggested text>

***Additional analyses for drug-induced liver injury***

The following additional analyses will be performed for drug-induced liver injury:

* Time to onset of the initial alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) during the treatment-emergent period will be analyzed using Kaplan-Meier method.
* A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
* For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

<End of suggested text>

Add sections as needed for study-specific safety parameters of interest. For oncology studies, add all specific parameters monitored as per NCI-CTCAE scale + grading, depending on the compound, study phase, etc. For biologic compounds, add a section for immunogenicity.

#### Product complaints (section to be removed if not applicable to the study)

This section is applicable only for studies where device is used to administer the IMP to describe the product complaints related to medical devices reported by investigator sites.

<Start of common text>

All product complaint summaries during the on-treatment period (see [Section](#_Ref84229018) 3.1) will be generated in the [safety/exposed] population with number (%) of participants experiencing at least one event as well as number of events and rate per 100 participant-[years/months].

Rate per 100 participant-[years/months] will be defined as the number of events divided by the cumulative duration of participants’ exposure expressed in [years/months] \*100.

The overview of product complaints with the details below will be generated:

* Any product complaint
* Any product complaint related to AEs
* Any product complaint leading to incorrect IMP dose administration

In addition, the analyses below will be conducted.

* Any product complaint categorized by type of complaint
* The number of product complaints by [country and site/site]
* AE(s) leading to product complaints by primary SOC and PT

<End of common text>

## Other analyses

This section should cover the analysis of PK, immunogenicity, quality of life, biomarkers, etc. Subsections can be added if needed. Suggested text is provided for the analysis of PK and immunogenicity.

### Other variables and/or parameters

#### PK analyses

<Start of suggested text for studies without NCA analysis >

To be included if no non-compartmental analysis (NCA) is performed by PK department. This section should be developed in close cooperation with PK function

Ctrough, Ct, Cfollow-up, Ceoi concentrations will be defined as follows:

* Ctrough is defined as concentration sample taken xx [days/h] ±xx [days/h] after previous administration
* Ct is defined as concentration sample taken xx [days/h] ±xx [days/h] after [previous administration/administration at xx] eg, first administration of a cycle
* Cfollow-up is defined as concentration sample taken xx [days/h] ±xx [days/h] after last administration
* Ceoi is defined as concentration sample taken at the end of infusion

Ctrough, Ct, Cfollow-up, Ceoi concentrations will be described [by actual intervention group/in the Compound number intervention group] on the PK population for each [planned visit/analysis window] using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum. These analyses will be performed by specific subgroups (eg, gender, BMI, age) if appropriate.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics. For the calculation of concentrations ratios, concentration values below the LLOQ may be replaced by LLOQ/2. Geometric mean will not be computed in case at least one concentration is below LLOQ.

<End of suggested text for studies without NCA analysis >

<Start of suggested text for studies with NCA analysis >

Following texts and sub-sections [Section](#_Ref76393383) 3.7.1.1.1 to [Section](#_Ref73628234) 3.7.1.1.8 to be included if non-compartmental (or other) analysis is performed by PK department. This section should be developed in close cooperation with PK function. Content-reuse from protocol, if applicable.

The PK parameters will be calculated using non-compartmental method from Compound number concentrations add matrix or analyte concentrations if applicable and will include but may not be limited to those listed in Table 13 (content-reuse from protocol).

Table 13 - List of PK parameters and definitions (content-reuse from protocol)

| Parameters | Definition |
| --- | --- |
| Cmax | Maximum concentration observed |
| Ct | Concentration taken xx [days/h] ±xx [days/h] after administration |
| Ceoi | Concentration at the end of infusion |
| tmax | Time to reach Cmax |
| Clast | Last concentration observed above the lower limit of quantification |
| tlast | Time of the last concentration observed above the lower limit of quantification (ie, Clast) |
| Ctrough | Concentration observed just before intervention administration during repeated dosing |
| AUClast | Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to tlast |
| AUC0-τ | Area under the concentration versus time curve over the dosing interval (T) |

These PK parameters will be summarized as indicated in following sections on the PK population.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics. Geometric mean will not be computed in case at least one concentration is below LLOQ.

Ctrough is defined as concentration sample taken xx [days/h] ±xx [days/h] after previous administration. Not applicable if Ctrough concentrations are taken into account regardless of sampling time deviations, dose delays, dose reductions or dose interruptions.

Detail potential exclusion rules of PK data by pharmacokineticist The pharmacokineticist may exclude a single parameter or a full profile parameters from the descriptive statistics and PK statistical analysis if the participant had a dose delay of at least xx days, dose reduction of at least xx%, dose interruption of at least xx hours.

If applicable, add details here for the computation of other parameters (eg, accumulation ratios between visits, metabolic ratio) calculated by B&P.

##### Descriptive statistics

The PK variables defined above will be summarized [by actual intervention group/in the Compound number intervention group/by dose level] [(by planned visit/analysis window if applicable)] using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum.

These descriptive statistics will be provided by PKDM department, except for specific plots (eg, for ctrough) and for other derived parameters (eg, Accumulation ratio (Rac) (Cycle Y to Cycle X ratio) for Cmax, AUC(s) or Ct )) for which individual values and descriptive statistics will be provided by B&P group.

For all the following statistical analyses, discuss their relevance with the PKist according to the type of administration of the intervention (eg, oral or IV) and the objectives of the study. Relevant PK parameters for SARxxxxxx, and metabolites if applicable, in particular AUC(s) need to be adapted (eg, AUClast, AUC0-T, partial AUC). Remove the subsections that are not applicable.

##### Dose effect

If dose effect should be assessed on specific PK parameters (eg, clearance), consider the following text after updating the relevant parameters. Remove gender from the model if not applicable, add covariates if applicable.

For CL, Compound number dose effect will be assessed with a linear model on the log-transformed parameter with dose and gender as fixed categorical effects.

Point estimate and 90% CI obtained, by dose level and overall, from this model will be converted back to the original scale using the antilog transformation.

##### Accumulation

Discuss other relevant parameters with PKist (eg, CEOI for infusion administration or Ctrough for late accumulation). Remove gender from the model if not applicable.

For Cmax and AUC(s), accumulation ratios will be assessed at Cycle X and Cycle Y separately with a linear model on the log-transformed ratio with dose and gender as fixed categorical effects.

Point estimate and 90% CI obtained, by dose level and overall, from this model will be converted back to the original scale using the antilog transformation.

Listings of participant accumulation ratios will be provided.

##### Dose proportionality

For Cmax and AUC(s), dose proportionality will be assessed using the empirical power model (pharmacokinetics parameter = α x doseβ), along with an “estimation” interpretation, according to the recommendations in Gough et al. (1995) [reference]:

Add the following reference to the list of references: Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry / pharmacokinetics UK joint working party. Drug Inf J. 1995;29:1039-48.

The power model will be fit on the log-transformed scale:

log(parameter) = log(α) + β ´ log(dose).

Model lack-of-fit will be assessed by residual plots, and by an F-test of the residual mean square versus the pure error residual mean square. If the model fit is adequate, point estimate and 90% CI for β will be obtained, and used to obtain point estimates and 90% CIs for the PK parameter increase associated with an r-fold (r = 2 and r = high dose / low dose) increase in dose, by exponentiating r to the power of the β point estimate and confidence limits,

r β ± t ´ SE(β).

If there is evidence of model lack-of-fit, then attempts could be made to fit the model over a reduced dose range (eg, excluding one extreme dose level).

Otherwise, a linear model on the log-transformed parameter with dose as fixed categorical effect will be used. Point estimate and 90% CI, associated with mean difference between pairwise dose increases, obtained from this model will be converted back to the original scale using the antilog transformation.

##### Food effect

In case of food effect objective (eg, for interventions administered orally), consider the following text. Remove gender from the model if not applicable.

Only participants evaluable for food effect will be included in the analysis. Food effect will be assessed comparing Cmax and AUC(s) between Cycle 1 Day 1 and Cycle 1 Day X. Data from participants with significant carry-over effect on Cycle 1 Day X will be excluded from the analysis, ie, when Ctrough is >5% from Cmax. An additional analysis may be considered on adjusted concentrations or parameters.

The mean difference between food conditions will be assessed with a linear model on the log-transformed parameter with food and gender as fixed categorical effects.

For the computation of the geometric means ratio of food conditions (fed/fasted), point estimate and 90% CI obtained from this model will be converted back to the original scale using the antilog transformation.

Furthermore, the distribution of tmax and tlag values for each food condition and of differences in tmax and tlag between food conditions (fed versus fasted) will be represented by histogram plots.

The food effect p-value on tmax and tlag will be provided, using the exact marginal homogeneity test for ordered categorical data. if relevant

##### Variance components

If estimation of variance components is relevant, consider the following text. Remove gender from the model if not applicable.

Within-participant and total standard deviations for log(Cmax) and log(AUC(s)) will be estimated by equating observed and expected means squares within the following linear model framework,

log(parameter) = Dose + Day + Day´Dose + Gender + Participant(Dose´Gender)

with fixed categorical effects for dose, day, gender and day-by-dose interaction, and with a random term for participant-within-dose-by-gender.

90% CIs will be computed using the simple c2 method for the within-participant SD, and the Graybill-Wang procedure [reference] for the total SD.

Add the following reference to the list of references: Burdick RK, Graybill FA. Confidence intervals on variance components. New York, United States of America: Marcel Dekker Inc.; 1992. p. 28‑57.

##### Drug-drug interaction

In case of drug-drug interaction objective in a specific cohort (eg, interaction with a CYP3A inhibitor for interventions administered orally) consider adapting the following text depending on the design used for this objective: the example text below is given for a cohort with a one-sequence cross-over with administration of tested drug alone in Period 1 and co-administration of tested drug and another drug in Period 2. Remove gender from the model if not applicable.

For Cmax and AUC(s) the mean difference between treatments (Compound number co-administered with xxxx and Compound number alone) will be assessed with a linear model on the log-transformed parameter with dose and gender as fixed categorical effects, if both SAR and the other treatment are taken by the same participant at different timepoints: and with an unstructured 2-by-2 matrix of treatment-specific variances and covariance for participant within gender blocks. In case of convergence problems, other variance-covariance structures will be explored.

Point estimates and 90% CI for the geometric means ratio of treatments (Compound number co-administered with xxxxxx/Compound number alone)will be obtained by computing point estimates and 90% CIs for the differences between treatment means within the linear model framework, and then converting to ratios by the antilog transformation.

Depending on the objective of the study regarding the demonstration of lack of interaction, consider adding the following paragraph.

Lack of interaction will be concluded if the 90% CI for the geometric means ratio of the PK parameter for Compound number is entirely within the [0.80; 1.25] acceptance range.

If any 90% CIs are not wholly contained within the [0.80; 1.25] acceptance range, then the clinical significance of such geometric means ratio estimates and 90% CI for Compound number will be interpreted within the context of the therapeutic index.

##### [Batch/formulation] effect

In case of change of batch or formulation during the study, consider the following text. Remove gender from the model if not applicable.

For AUC(s), [batch/formulation] effect for dose xxx will be assessed with a linear model on the log-transformed parameter with [batch/formulation] and gender as fixed categorical effects.

Point estimate and 90% CI obtained from this model will be converted back to the original scale using the antilog transformation.

##### Day xx versus Day 1 4β-hydroxycholesterol ratio

In case of 4β-hydroxycholesterol evaluation (eg, for interventions administered orally), consider the following text. This section should be moved to biomarkers section if 4β-hydroxycholesterol ratio is identified as a biomarker endpoint in the protocol. Remove gender from the model if not applicable.

Individual values and Day XX / Day 1 ratios of 4b-hydroxycholesterol will be listed and summarized by day using descriptive statistics by dose level and overall.

The log-transformed Day XX / Day 1 ratio will be analyzed using a linear model on the log-transformed ratio with dose and gender as fixed categorical effects and log-transformed concentration on Day 1 (baseline) as continuous covariate.

Point estimate and 90% CI obtained, by dose level and overall, from this model will be converted back to the original scale using the antilog transformation.

<End of suggested text for studies with NCA analysis >

Section to be removed if not applicable to the study.

#### Immunogenicity analyses

<Start of common text>

Participant’s ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the ADA population for each ADA assayed (eg, neutralizing ADA), separately.

Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately. Time to ADA onset and duration of ADA will be described with minimum, Q1, median, Q3 and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

Sample status (negative, positive, inconclusive) and titers will also be described overtime using descriptive statistics.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

***Participant’s ADA status***

* Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
* Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
* Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including participants without pre-treatment samples).
* Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant. A 2-fold or 3-fold serial dilution schema should be applied during titration. A difference in titer values of two titer steps between an on intervention or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2-fold serial dilution schema (or 9-fold increase in titers for 3-fold serial dilution schema)
* Participants with **unclassified ADA** correspond to participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (ie, a positive ADA sample during the TE period in a participant with pre-existing ADA but with missing titer at this sample or at baseline).
* Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample nor unclassified ADA during the TE period.
* Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.
* Participants with cross-reactivity with endogenous protein(s) and/or cross-neutralization of endogenous protein(s)
* Participants with ADAs (and NAbs) directed against a specific domain (within multi-domain biologics)

***Kinetics of ADA response*** (to be included if applicable, ie, study duration from first IMP administration is at least 6 months)

Kinetics of ADA response will be derived for participants with treatment-induced/boosted ADA considering ADA samples collected during the TE period and post-treatment period.

* **Time to onset of ADA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.
* **Duration of ADA response** is defined as the time between the first treatment-induced/ boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ADA duration will be summarized only for participants with persistent ADA response.
* A positive sample (boosted positive sample for participants with pre-existing ADA) occurring after the TE period will be considered as treatment-induced/boosted ADA if a previous treatment-induced/boosted ADA occurred during the TE period and less than 16 weeks before this sample; indeed a treatment-induced/boosted ADA occurring at the end of the TE period could have positive samples after the TE period due to half-life of the immunoglobulin G
* **Persistent ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
* **Transient ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of less than 16 weeks and the last sample of the TE period is not treatment-induced/boosted.
* **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

***ADA response variable:***

* **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.

<End of common text>

Sections to be added as appropriate.

#### Quality of life analyses

Enter Quality of Life Analyses

#### Biomarker analyses

Enter Biomarker Analyses

#### Concentration-QT analyses

<Start of example text >

This section provides guidance on statistical analyses required to assess the absence of QT prolongation effect using thorough ECG monitoring concurrently to PK samples. Discuss the need for such analyses depending on the study objectives. Example text is provided below for a dose escalation study without intra-patient dose escalation and should be updated if such analyses is conducted for other study designs (eg, intra-patient dose escalation). PCSA or Heart Rate evolution over time from thorough ECG monitoring should also be described in the safety section. Remove the section if not applicable.

All the analyses will be performed on the Concentration-QT population, based on ECG extracted from add ECG method considering QTcF, heart rate (HR), PR and QRS intervals as ECG parameters and Compound number PK concentrations (also plan for analysis on metabolite concentrations if relevant). Post-dose concentrations below the lower limit of quantification (LLOQ) will be imputed to LLOQ/2.

*Validation of QT correction*

The validation of the QT correction method (QTcF interval is independent from HR) will be done using scatter plots of QTcF vs HR (or RR if available) considering pre-treatment data.

*Descriptive statistics*

Descriptive statistics of change from baseline overtime in ECG parameters and of PK concentrations will be computed by dose level.

*Exploratory plots*

In order to investigate any potential delayed or sustained effects and the type of modeling to be done, the relationship between the change from baseline in ECG parameters and PK concentrations will be first explored graphically:

* Plot of mean (± SE) change from baseline in ECG parameters and mean PK concentration versus time (hours post-dose) by dose level, overlaid onto the same plot
* Hysteresis plot of mean change from baseline in ECG parameters and PK concentrations by dose level

*Modeling*

In case of direct and linear relationship, a linear model will be carried out on the change from baseline in ECG parameter with time as fixed categorical effect, PK concentration (slope) and centered baseline ECG parameter (individual baseline minus mean baseline value of the population) as fixed continuous covariates, and with random terms for individual participant deviation from the population intercept and slope (with an unstructured variance-covariance matrix per participant).

The estimates of each effect of the model, along with their 90% CI, will be provided. In addition, prediction (estimates and 90% CIs) of change from baseline in ECG parameters at selected concentrations (geometric mean Cmax for each dose) will also be calculated from the model. The scatter plot of individual ECG parameters values versus PK concentrations with the regression line overlaid and its 90% CI will also be provided.

Goodness-of-fit will be evaluated using plots. If the model assumptions are not met or in case of lack of fit (ie, the linear model is not adequate), alternative models like non-linear models (eg, exponential, Emax) and/or model averaging methods [reference] might be explored.

Add the following reference to the list of references: Sébastien B, Hoffman D, Rigaux C, Pellissier F, Msihid J. Model averaging in concentration-QT analyses. Pharm Stat. 2016 Nov;15(6):450-58.

<End of example text >

#### Other PK/PDy analyses

In case of advanced methods for PK/PDy analyses (including for instance specific statistical models or several steps with variables selection), a dedicated PK/PDy SAP should be prepared and it can be referred in this section. Otherwise, state briefly which PDy endpoints for safety or efficacy will be assessed and which type of analysis will be run. Remove the section if not applicable.

Enter Other PK PDy Analyses

#### XXX

### Subgroup analyses

This section describes the statistical approaches for subgroup analyses. For most of the studies, subgroup analyses will only be performed on the primary efficacy endpoint (see example below) and potentially on a key secondary endpoint. In rare situations (very large studies), subgroup analyses may also be done on safety endpoints.

Consider pooling the small subgroups to have reasonable size to have the meaningful estimation. When interaction p-values are presented (only applicable to subgroup analyses conducted on efficacy endpoints), they must be interpreted with consideration of the multiplicity issue. In addition, in case different treatment effects are observed in subgroups, adjusted analyses may be performed to investigate for confounding factors.

If no subgroup analyses are performed (eg, for ph1 studies), indicate “Not applicable”.

<Start of example for subgroup analyses of primary efficacy endpoint >

Subgroup analyses of the primary efficacy endpoint will be performed to assess the homogeneity of the treatment effect across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

* Race (White, Black or African American, Asian, Other).
* Ethnicity (Hispanic, Not Hispanic).
* Age group (<50, 50 to <65, ≥65 years)
* Gender (Male, Female).
* Baseline body mass index (BMI) level (<30, ≥30 kg/m²).
* Baseline HbA1c (≤8.5%, >8.5%).

It is recommended to perform subgroup analyses using a separate model for each subgroup (eg, one model for the analysis in Male, one model for the analysis in Female). Results are to be presented for all subgroups of the factor rather than in a subset (eg, if the analysis is done in Male, the analysis is also to be done in Female).

In case of special need or regulatory agency request, if treatment effects will be provided with a single model for all categories of the subgroup factor (eg, a single model for the subgroup analysis including participants from both Male and Female subpopulation), please include text similar to the following paragraph.

Treatment-by-subgroup interaction term and the subgroup factor term will be added in the primary model. In the case that the subgroup factor is identical or similar to a randomization strata factor, the strata factor will not be kept in the model.

The treatment effects (Compound number versus placebo) for the primary endpoint will be provided, as well as the corresponding 95% CI, for each subgroup, using the same method as applied to the primary analysis. Forest plots will be provided.

<End of example for subgroup analyses of primary efficacy endpoint >

## Interim analyses

This information will be copied from the protocol. Additional details may be added.

The following information belongs to this section:

* The reason for conducting IAs and their impact on the conduct of the study. Could be a formal IA or an early analysis (eg, when comprehensive analysis of the primary endpoint can be performed before the end of the study) for submission purpose with no impact on the conduct of the study. For early phase oncology studies, analysis to determine the recommended phase 2 dose at end of dose escalation part and analysis at end of each cohort during dose escalation do not belong to this section.
* The timing of IAs (eg, number of participants, number of participants completing a certain number of visits, calendar time, number of events reached, etc).
* Analyses to be performed at the time of IAs (eg, endpoints included, statistical analysis methods, safety summaries etc).
* The cut-off date and how the analyses will be performed (eg, management of participants still receiving intervention at the time of the cut-off date, analysis periods truncation, management of AEs occurring after the cut-off date, management of AEs starting before the cut-off date but leading to intervention discontinuation or death after the cut-off). The use of an analysis cut-off date is not systematic and to be discussed with the study team according to the objective of the analysis.
* Any actions resulting from an IA such as sample size re-estimation or stopping rules
* Multiplicity considerations relating to the interim and final analyses
* Blinding/ unblinding strategy
* Results of simulations, as appropriate

<Start of example text for formal interim analyses>

Two interim analyses (IA) are planned, when xx% and xx% of the total number of expected events have occurred:

* Interim analysis for futility will be conducted when approximately xxx events (xx% of the targeted number of primary endpoint events) have occurred
* Interim analysis for [futility and overwhelming efficacy] will be conducted when approximately xxx events (xx% of the targeted number of primary endpoint events) have occurred.

The IAs will be performed by an external independent statistician (not involved with the conduct of the study). Further details are described in the DMC charter. The results of the IAs will be provided to the DMC by the independent statistician.

Control of the type I and type II error will be ensured using Gamma (-x) spending function for type II error (futility) and Gamma (-x) for type I error (efficacy) at each IA. The choice of non-binding nature of the futility stopping boundary ensures that the efficacy stopping boundaries are not affected regardless of whether the futility guidance is followed or not.

Table 14 shows the stopping rules at each IA. Since the observed number of events at the IAs may not be exactly equal to the planned number of events, the efficacy and futility boundaries will be recalculated using the pre-specified α and β-spending functions and based on the actual number of observed events at the IA and the total number of targeted events to calculate the exact information fraction.

Table 14 - Interim analyses stopping boundaries

| Timing of analyses | Stopping boundaries  (1-sided p-value) boundaries can also be provided on Z-statistic scale or HR | |
| --- | --- | --- |
| Futility | Overwhelming efficacy |
| First IA: xx% of targeted events | p >0.xxx | Not applicable |
| Second IA: xx% of targeted events | p >0.xxx | p <0.xxx |
| Calculations done using EAST® 5.4 | | |

Simulations were conducted under several HR scenarios to determine the probability to stop the study at IA either for futility or overwhelming efficacy (Table 15). Suggest including simulation details in appendix if it is too long.

Table 15 - Simulated probabilities to stop for futility or efficacy at the interim and final analyses

| Scenario | Look | # of Events | Simulated cumulative probabilities (%) | | Simulated incremental probabilities (%) | |
| --- | --- | --- | --- | --- | --- | --- |
| Stop for efficacy | Stop for futility | Stop for efficacy | Stop for futility |
| Under H0 (HR=1) | 1st IA (futility) | xx | - | xx | - | xx |
|  | 2nd IA (futility and efficacy) | xx | xx | xx | xx | xx |
|  | Final | xx | xx | - | xx | - |
| Under H1 (HR= xx) | 1st IA (futility) | xx | - | xx | - | xx |
|  | 2nd IA (futility and efficacy) | xx | xx | xx | xx | xx |
|  | Final | xx | xx | - | xx | - |
| Under HR= xx | 1st IA (futility) | xx | - | xx | - | xx |
|  | 2nd IA (futility and efficacy) | xx | xx | xx | xx | xx |
|  | Final | xx | xx | - | xx | - |
| Note: Simulation were performed in EAST® 5.4 with number of simulations = xx and seed = xx | | | | | | |

<End of example text>

<Start of example text for early analyses>

The study analysis will be conducted in two steps. The first step analysis will be conducted when to be completed. The common cut-off date for the first-step analysis is defined as to be completed. The final analysis will be conducted at the end of the study.

<End of example text>

<Start of example text that apply to both early analyses and formal interim analyses>

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for analyses performed at [first step analysis/interim analysis]:

* Participants without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
* Participants who did not complete treatment period nor prematurely discontinued the study intervention at cut-off date will be analyzed as “ongoing” in the disposition summary.
* Their TE period, treatment period and concomitant medication period will end at the cut-off date.
* Their treatment duration will be derived by considering date of cut-off as last IMP date.
* Analyses of number of IMP administration, mean administration frequency, and compliance will be performed up to the last IMP administration reported in the e-CRF up to the cut-off date.
* AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an AE starting prior to the cut-off date will be taken into account. Medications, intervention discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses. It is recommended to apply a data cut-off for analyses for submission purpose

<End of example text>

<Start of example text for early phase oncology studies >

No formal interim analyses are planned. However, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the dose expansion part of the study, eg, after 15 participants have undergone at least 2 post-baseline tumor assessments or have discontinued the study intervention, whichever is earlier.

<End of example text for early phase oncology studies >

## Changes to protocol-planned analyses

The purpose of this section is to document the major changes to the statistical analysis features from a protocol version to another. The changes themselves should be incorporated into the relevant sections of this document. If there were no important changes to the protocol planned analyses, please delete this appendix.

If the changes are part of an amended SAP, there will be some overlap with version history, though more justification (for regulatory) may be provided here. Changes made after database lock are out of scope for this document.

Additional analyses (which do not replace/modify the planned analyses) or clarifications are generally not considered as major changes.

<Start of suggested text>

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

| Amendment Number | Approval Date | Changes | Rationale |
| --- | --- | --- | --- |
|  | dd-mmm-yyyy |  |  |
|  |  |  |  |
|  | | | |

<End of suggested text>

<Start of example text>

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

| Amendment Number | Approval Date | Changes | Rationale |
| --- | --- | --- | --- |
| 1 | 12-Jul-2009 | Primary analysis changed from unstratified log-rank to log-rank stratified by center (randomization stratification factor) | FDA Special Protocol Assessment comments |

<End of example text>

# Sample size determination

The information will be copied from the protocol. Additional details may be added to further describe the sample size calculation methods. To facilitate automatic translations into other language, it is recommended to simplify description with all the sample size elements as bullet points.

Enter Sample Size Determination

# Supporting documentation

The appendix/appendices can include important information not included in the body text of the SAP, for example:

* Participant disposition
* Baseline characteristics and demographics
* Medical history
* Prior/concomitant/follow-up medications (including dictionary)
* Data derivation rules if needed

## Appendix 1 List of abbreviations

ADI: actual dose intensity

AE: adverse event

AESIs: adverse events of special interest

ALT: alanine aminotransferase

ANCOVA: analysis of covariance

BMI: body mass index

ECG: electrocardiogram

e-CRF: electronic case report form

HDL-C: high density lipoprotein cholesterol

HGLT: high level group term

HLT: high level term

HR: hazard ratio

IA: interim analysis

IMP: investigational medicinal product

ITT: intent-to-treat

LDL-C: low density lipoprotein cholesterol

LLT: lower-level term

MedDRA: medical dictionary for regulatory activities

NCI-CTCAE: National cancer institute common terminology for adverse events

PCSA: potentially clinically significant abnormality

PDI: planned dose intensity

PK: pharmacokinetic

PT: preferred term

RDI: relative dose intensity

SAE: serious adverse event

SAP: statistical analysis plan

SD: standard deviation

SOC: system organ class

TE: treatment-emergent

TEAE: treatment-emergent adverse event

TG: triglycerides

WHO-DD: World Health Organization-drug dictionary

## Appendix 2 Participant dispositions

This section provides the description of the populations for analyses as well as the disposition of participants at the end of the intervention and end of the study.

<Start of common text>

The number (%) of participants included in each of the analysis populations listed in Table 7 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently [enrolled/randomized]. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The following definitions of intervention discontinuations are applicable to combination studies (ie, studies with combination intervention) where some interventions of the combo can be continued while other(s) are discontinued. For other studies (monotherapy studies and combination studies where all interventions are stopped at the same time), no definition needs to be provided.

Regarding intervention discontinuation, the following definitions will be used:

* Permanent **partial** intervention discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued
* Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs (not necessarily at the same time: eg, in a two-drug combination study, when the first drug is permanently discontinued and the intervention with the second drug is allowed to continue, full intervention discontinuation occurs when the second drug is stopped)

The number (%) of participants in the following categories will be provided:

* [Enrolled/Randomized] participants
* [Enrolled/Randomized] but not exposed participants
* [Enrolled/Randomized] and exposed participants
* Participants still on study intervention
* Participants who completed the study treatment period as per protocol to be removed if not applicable, eg, oncology studies where the IMP is to be administered until disease progression
* Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation. for monotherapy studies
* Participants who did not complete the study treatment period as per protocol and main reason for permanent full intervention discontinuation. for combination studies, ie, studies with a combination intervention. When all interventions are not discontinued at the same time, the reason for permanent full discontinuation is the reason for discontinuation of the last intervention(s) stopped
* Participants who did not complete the study treatment period as per protocol for intervention XXX and main reason for permanent partial intervention discontinuation (discontinuation of intervention XXX). applicable to combination studies where some interventions of the combo are continued while other(s) are discontinued. In such case, the reason for discontinuation of the intervention of interest may be described
* Participants who completed the study period as per protocol.
* Participants who did not complete the study period as per protocol and main reason for study discontinuation if information collected in the eCRF.

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19, if applicable.

The number (%) of exposed and not [enrolled/randomized] participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, [enrolled/randomized], with permanent full intervention discontinuation and with early study discontinuation will be provided by [country and site/geographical region, country and site]. Mandatory for submission in EU. Number of participants randomized/enrolled by country also mandatory for Eudract

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the [randomized/enrolled/exposed] population as well as displayed separately as related versus not related to COVID-19 if applicable.

<End of common text>

## AppenDix 3 Demographics and baseline characteristics, prior or concomitant medications

Briefly define the analysis of demographics and baseline characteristics, prior or concomitant medications. In general, it is not recommended having p-value calculation for intervention difference for demographics and baseline characteristics data unless requested by health authorities.

<Start of common text>

***Demographics, baseline characteristics, medical surgical history***

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the [randomized/enrolled/exposed] population.

Demographic and baseline characteristics

* age in years as quantitative variable and in categories (<65, 65 to <75, ≥75) modify the age categories as needed, for example, age 85 could be the cutoff as requested by agency
* gender (Male, Female, intersex)
* race (White, Black or African American…) be consistent with eCRF. Sub-category can be also displayed, if any. If several races are collected for a participant, a category of “Multiple” should be also displayed
* ethnicity (Hispanic or Latino, not Hispanic or Latino)
* Other baseline characteristics to add (ie, randomization strata, weight, BMI, etc)

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes XXX to be completed according to the protocol. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version [currently in effect at Sanofi at the time of database lock/X.X] Specify MedDRA version if known and fixed due to project specifics

<End of common text>

<Start of suggested text for non-oncology study>

Specific disease history includes time from diagnosis, severity of the disease To be completed according to the protocol

<End of suggested text for non-oncology study>

<Start of suggested text for oncology study>

Specific disease history includes primary tumor site, histology or histopathology type, TNM, staging, time from initial diagnosis to randomization (in weeks or months), ... To be completed according to the protocol

Specific disease status at study entry includes extent of diseases, number and type of organs involved, … To be completed according to the protocol

Other baseline characteristics include ECOG performance status.

<End of suggested text for oncology study>

<Start of common text>

***Prior or concomitant medications***

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version [currently in effect at Sanofi at the time of database lock/X.X]. Specify WHO-DD version if known and fixed due to project specifics

* Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
* Concomitant medications are any medications received by the participant concomitantly to [the/any] IMP[(s)] [during the on-treatment period/from the first administration of IMP to the last IMP intake + X days]. In general, it is recommended to use the same X as for the on-treatment period definition.
* Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
* A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the [enrolled/randomized] and exposed population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

<End of common text>

<Start of example text for oncology>

***Anticancer therapies***

Prior anticancer therapies include chemotherapy, hormonotherapy, surgery, radiotherapy, bone marrow transplant, targeted therapies, radiation therapy etc. To be completed according to indication or study specifics

Provide detailed variables described by type of anticancer therapy. The number of different regimens will be described.

Further therapies after discontinuation of intervention will be summarized based on WHO-DD coding.

TNT is defined as the time from randomization to the start of further anticancer therapy. Participants who do not receive any further anticancer therapy before the cut-off date will be censored at to be completed. TNT will be analyzed using Kaplan-Meier method.

<End of example text>

## Appendix 4 Data handling conventions

It is recommended to put major data handling conventions under this section, such as analysis window rules or visit data mapping/allocation, whether data from unscheduled visits are to be used or not in analysis or baseline definition.

<Start of example text>

**Analysis windows for time points**

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, PK and ADA variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 16 - Analyses window definition

| Scheduled visit post baseline | Targeted study day | Analysis window in study days |
| --- | --- | --- |
| Week 1 (Visit 4) | 7 | 2 to 17 |
| Week 4 (Visit 5) | 28 | 18 to 41 |
| Week 8 (Visit 6) | 56 | 42 to 69 |
| Week 12 (Visit 7) | 84 | 70 to 104 |
| Week 18 (Visit 8) | 126 | 105 to 153 |
| Week 26 (Visit 9) | 182 | ≥154 |
| Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed). | | |

**Unscheduled visits**

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the last on-treatment value, analysis according to [PCSAs/NCI grades/PCSAs and NCI grades], and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

<End of example text>

# References

References to both internal and external documents and publications should be listed in alphabetical order. Do not reference internal reports in preparation.

In the reference list, use the style and format published by the International Committee of Medical Journal Editors [ICMJE, 1991]. Citations to external documents and publications should be indicated in the text by citing the author and year within parentheses. For example, the in-text citation for the reference included would be (Hatcher et al, 2007).

<Start of example>

Lin DY, Wei LJ. The robust inference for the Cox proportional-hazards model. J Am Stat Assoc. 1989;84:1074-8.

<End of example>