NOVARTIS

Clinical Development

BYL719/Alpelisib

CBYL719C2202 / NCT04899349

EPIK-B4: A Phase II, multicenter, randomized, open-label, active-controlled study to assess the safety and efficacy of dapagliflozin + metformin XR versus metformin XR during treatment with alpelisib (BYL719) in combination with fulvestrant in participants with HR+, HER2-, advanced Breast Cancer with a PIK3CA mutation following progression on/after endocrine-based therapy

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
05-Oct-2021	Prior to FPFV	Creation of final version	N/A - First version	NA
29-Mar-2023	Prior to DBL	Permanent halt of recruitment and early termination of study	Removed primary analysis, instead the primary endpoint will be summarized descriptively. Reduced number of analyses and summaries on primary, secondary and safety endpoints.	Section 1-5

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AE	Adverse event
AESI	Adverse event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BOR	Best overall response
CBR	Clinical benefit rate
CI	Confidence Interval
CR	Complete response
CRF	Case Report Form
CRS	Case retrieval strategy
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DI	Dose Intensity
DRL	Drug Reference Listing
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FPFV	First patient first visit
GI	Gastrointestinal
HLGT	High level group term
HLT	High level terms
HR	Hormone Receptor
IRT	Interactive Response Technology
ITT	Intent To Treat
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not evaluable
OL	Open-label
ORR	Overall response rate
PD	Progressive disease
PDI	Planned dose intensity
PFS	Progression-free survival
PIK3CA	Phosphoinositide-3-kinase catalytic subunit alpha

PR	Partial response
PT	Preferred term
QTcF	Corrected QT interval (corrected by Fridericia's formula)
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SMQ	Standardized MedDRA queries
SOC	System organ class
TA	Tumor assessment
TBIL	Total bilirubin
UNK	Unknown
WHO	World Health Organization
XR	Extended Release

1 Introduction

This document describes the detailed statistical methodology to be used for the clinical study report (CSR) for the analysis of study CBYL719C2202, a Phase II, multicenter, randomized, open-label, active-controlled trial designed to assess the safety and efficacy of the combination of dapagliflozin plus metformin XR compared to metformin XR alone during treatment with alpelisib plus fulvestrant in participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation following progression on or after endocrine-based therapy.

The content of this SAP is based on the CBYL719C2202 protocol amendment 1 released on 06-Aug-2021. All decisions regarding analyses, as defined in this document, have been made prior to the database lock. Due to the permanent halt of recruitment and early termination of study, the primary analysis will not be conducted. Further changes to the protocol specified analyses are listed in Section 4.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specification (PDS), respectively.

Statistical Outputs and corresponding data structures required for Clinical Disclosure of Trial Results will also be described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specification (PDS), respectively.

1.1 Study design

Study CBYL719C2202 is a Phase II, multicenter, randomized, open-label, active-controlled trial designed to evaluate the safety and efficacy of the combination of dapagliflozin plus metformin XR compared to metformin XR alone during treatment with alpelisib plus fulvestrant, in participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation following progression on or after endocrine-based therapy. The study will only include participants who have at least one of the following baseline risk factors for the development of severe hyperglycemia:

- Diabetes (fasting plasma glucose (FPG) ≥ 126 mg/dL or ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5%)
- Pre-diabetes (FPG ≥ 100 mg/dL to < 126 mg/dL or 5.6 to < 7.0 mmol/L and/or HbA1c 5.7 to < 6.5%)
- Obesity (BMI ≥ 30)
- Age ≥ 75 years

Approximately 132 participants was planned to be randomly assigned to one of the following treatment arms in a 1:1 ratio to receive either:

- Arm A: Alpelisib + fulvestrant + dapagliflozin + metformin XR
- Arm B: Alpelisib + fulvestrant + metformin XR

Randomization to treatment will be stratified by diabetic status at baseline, i.e., normal vs pre-diabetic/diabetic (based on FPG and/or HbA1c laboratory values).

The primary analysis will not be performed due to the permanent halt of recruitment and early termination of study. Only a final descriptive analysis will be conducted at the end of study (see Protocol Section 9.3).

No Data Monitoring Committee is planned for this study.

Figure 1-1 Study design

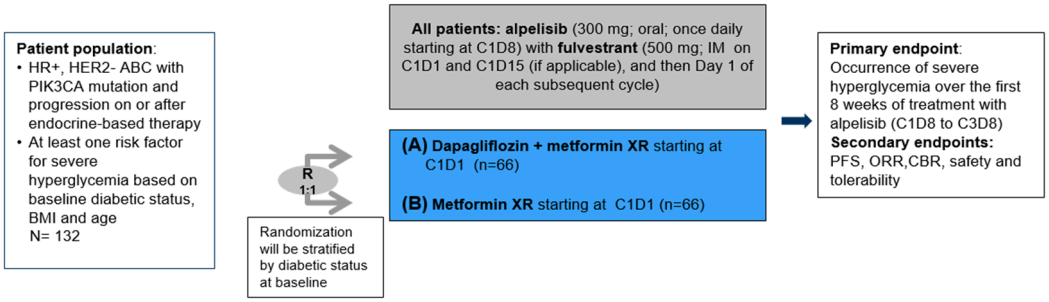
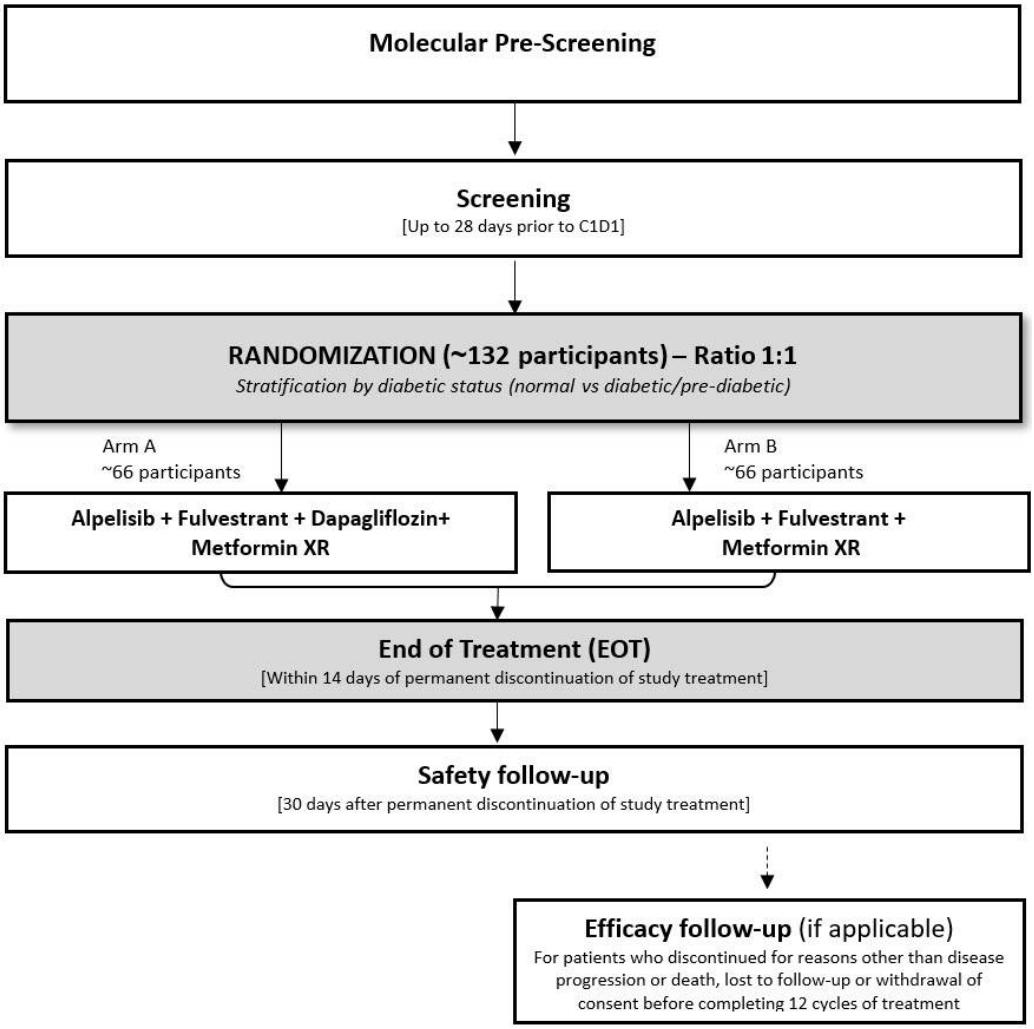


Figure 1-2 Study flow



1.2 Study objectives, endpoints and estimands

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the reduction in severe hyperglycemia events over the first eight weeks of alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR	• Occurrence of severe hyperglycemia (grade ≥ 3, based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant treatment (from C1D8 to C3D8)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR with regard to preliminary efficacy parameters	• PFS, ORR with confirmed response and CBR with confirmed response, based on local radiology assessments and using RECIST 1.1 criteria
• To assess the safety and tolerability	• Safety: Incidence, type, and severity of adverse events per CTCAE version 4.03 criteria including changes in laboratory values, ECOG, vital signs, liver assessments, renal and cardiac assessments Tolerability: dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
[redacted]	

1.2.1 Primary estimand

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary scientific question of interest is: what is the effect on the occurrence of severe hyperglycemia (based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant (from Cycle 1 Day 8 to Cycle 3 Day 8) with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR, for participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, which progressed on or after endocrine-based therapy and have at least one risk factor for severe hyperglycemia, regardless of additional antihyperglycemic therapies as needed?

The justification for targeting this treatment effect is that we wish to assess the treatment effect based on the occurrence of severe hyperglycemia while the participants are exposed to alpelisib plus fulvestrant as well as after the discontinuation and interruption of prophylactic antihyperglycemic therapies, since any discontinuation or interruption will reflect clinical practice.

The primary estimand is characterized by the following attributes:

1. Population: participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after endocrine-based therapy and have at least one risk factor for severe hyperglycemia; randomized and received at least one dose of study treatment.

   Note: at least one dose of study treatment refers to at least one dose of any component of alpelisib, fulvestrant, dapagliflozin + metformin XR or metformin XR.
2. Treatment: the first study treatment is alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR (plus additional antihyperglycemic therapies as needed). The second study treatment is alpelisib plus fulvestrant with prophylactic metformin XR (plus additional antihyperglycemic therapies as needed).
3. Variable: occurrence of severe hyperglycemia (Grade ≥ 3, based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant treatment (from Cycle 1 Day 8 to Cycle 3 Day 8). Further details are provided in Section 2.5.1.
4. Handling of remaining intercurrent events:
   - Discontinuation of alpelisib for any reason or not receiving any alpelisib will be handled using treatment policy strategy.
   - Discontinuation and/or interruption of prophylactic antihyperglycemic therapies for any reason will be handled using treatment policy strategy.
   - Dose interruption and/or reduction of alpelisib for any reason will be handled using treatment policy strategy.

   Details on how to handle intercurrent events are provided in Section 2.5.3.
5. Summary measure: difference between treatment arms in percentage of participants with severe hyperglycemia.

   Note: the primary analysis will not be performed due to the permanent halt of recruitment and early termination of study. Further details on the summary measure are provided in Section 2.5.2.

2 Statistical methods

2.1 Data analysis general information

The analyses will be performed by Novartis. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures, and listings.

Data included in the analysis

For the analysis, a cut-off date will be established after the follow-up has been documented. All statistical analyses will be performed using all data collected in the database up to the data

cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of participants enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

Study treatment will refer to both alpelisib + fulvestrant + dapagliflozin + metformin XR and alpelisib + fulvestrant + metformin XR.

2.1.1.2 Date of first administration of study treatment component

The date of first administration is defined as the first date when a non-zero dose of that component of study treatment is administered and recorded on "Study Treatment" eCRF (for fulvestrant) or "Study Treatment Summary" eCRF (for alpelisib/dapagliflozin/metformin XR) for that component of study treatment.

2.1.1.3 Date of last administration of study treatment component

The date of last administration is defined as the last date when a non-zero dose of that component of study treatment is administered and recorded on the "Study Treatment" eCRF (for fulvestrant) or "Study Treatment Summary" eCRF (for alpelisib/dapagliflozin/metformin XR) for that component of study treatment.

2.1.1.4 Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of any component of study treatment (alpelisib or fulvestrant or dapagliflozin or metformin XR) is administered. The date of first administration of study treatment will also be referred to as the start of study treatment.

For example: if the first dose of alpelisib is administered on 08-Jan-2022, first dose of fulvestrant is administered on 01-Jan-2022, and first dose of dapagliflozin and metformin XR is taken on 03-Jan-2022, then the date of first administration of study treatment is 01-Jan-2022.

2.1.1.5 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of any component of the study treatment (alpelisib or fulvestrant or dapagliflozin or metformin XR) is administered.

For example: if the last dose of alpelisib and fulvestrant is administered on 15-Apr-2022, and the last dose of dapagliflozin and metformin XR is taken on 17-Apr-2022, then the date of last administration of study treatment is on 17-Apr-2022.

2.1.1.6 Study day

The study day describes the day of the event or assessment date, relative to the reference start date.

The reference start date is designated as Study Day 1. Study Day –1 is the day that precedes Day 1. Study Day 0 is not defined. Study day is not to be used in numerical computations, for example in calculating exposure.

The study day will be calculated as follows:

- The date of the event (visit date, onset date of an event, assessment date etc.) - reference start date + 1 if the event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) - reference start date if the event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, disease progression, tumor response and ECOG performance status) is the date of randomization. (Example: if randomization date is 15-Dec-2021, start of study treatment is on 18-Dec-2021, and the date of death is 28-Dec-2021, then the study day when the death occurred is 14).

The study day will be displayed in data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.1.7 Time Unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.1.8 Baseline

For efficacy evaluations, the last available assessment, including unscheduled assessments, on or before the date of randomization is taken as the “baseline” value or “baseline” assessment. In the context of baseline definition, the efficacy evaluations also include ECOG performance

status. For RECIST-based endpoints only, including PFS, ORR and CBR, a window of 7 days after the start of study treatment will be allowed, i.e. the investigator assessed responses will be considered as a candidate for the baseline assessment if the assessment is within 7 days after the treatment start date.

For safety evaluations (i.e. laboratory assessments, ECGs and vital signs), the last available assessment, including unscheduled assessments, on or before the start date of study treatment as described in Section 2.1.1.4 is taken as "baseline" assessment. Assessments specified to be collected post-dose on the first date of treatment are not considered as baseline values.

If participants have no value as defined above, the baseline result will be considered missing.

2.1.1.9 On-treatment assessment/event

An on-treatment assessment event is defined as any assessment event in the following time interval:

- [date of first administration of study treatment; date of last administration of study treatment + 30 days], i.e. including the lower and upper limits

Note: the calculation of study treatment duration will use different rules as specified in Section 2.4.2.

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events.

An AE starting in the screening phase and ongoing in the on-treatment phase will not be considered an on-treatment AE unless it has worsened in severity.

If the last date of study treatment is missing, any assessment/event occurring after the start date of study treatment will be considered as on-treatment.

Data listings will include all assessments/events, flagging those which are not on-treatment assessments/events.

Note: The date of first administration of study treatment and the date of last administration of study treatment are defined in Section 2.1.1.4 and Section 2.1.1.5, respectively.

2.1.1.10 Windows for multiple assessments

In order to summarize ECOG and other data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows (except for ECOG, see Section 2.6.1 for ECOG-specific rules): If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Time windows for ECOG assessments is listed in Table 2-4.

2.2 Analysis sets

The Full Analysis Set (FAS) is comprised of all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The FAS will be the population for all efficacy analyses.

The Safety Set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any component of alpelisib, fulvestrant, dapagliflozin + metformin XR, metformin XR). Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received. The safety set will be the analysis set for all safety analyses.

2.2.1 Patient classification

Participants may be excluded from the analysis sets defined above based on the protocol deviations entered in the database and/or on specific participant classification rules defined in Table 2-1.

Table 2-1 Participant classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviation criteria leading to exclusion	Non-protocol deviation criteria leading to exclusion
FAS	No written informed consent	Not applicable
Safety set	No written informed consent	No dose of study treatment

2.2.2 Withdrawal of informed consent/opposition to use data/biological samples

Any data collected in the clinical database after a participant withdraws informed consent/ opposition to use data/biological samples from all further participation in the trial, will not be included in any analysis. The date on which a participant withdraws full consent is recorded in the eCRF. When an end of treatment visit occurs after withdrawal of informed consent/opposition to use data/biological samples, the end of treatment disposition status and reasons are retained.

Additional data for which there is a separate informed consent (such as pregnancy outcomes reporting consent, if applicable), collected in the clinical database without having obtained that consent will not be included in the analysis.

Any data that will be excluded will be identified by the presence of the appropriate protocol deviation criterion.

2.2.3 Subgroups of interest

No subgroup analysis will be performed.

2.3 Participant disposition, demographics and other baseline characteristics

Demographic data will be summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

2.3.1 Participant disposition

Enrollment by country and center will be summarized for all screened participants and also by treatment group using the FAS. The number (%) of randomized and treated participants included in the FAS will be presented overall and by treatment group. The number (%) of screened but not-randomized participants and the reasons for screening failure will also be displayed. The number (%) of participants in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS participants):

- Number (%) of participants who were randomized (based on data from IRT system)
- Number (%) of participants who were randomized but not treated (based on 'Study Treatment' and "Study Treatment Summary" eCRF not completed for any study treatment component)
    - Primary reason for not being treated (based on 'Treatment disposition' eCRF)
    - Number (%) of participants who were treated (based on 'Study Treatment" or "Study Treatment Summary" eCRF of each study treatment component completed with non-zero dose administered)
    - Number (%) of participants who are still on-treatment (based on the 'Treatment disposition' eCRF not completed);
    - Number (%) of participants who discontinued the study treatment phase (based on the 'Treatment disposition' eCRF)
- Primary reason for study treatment phase discontinuation (based on the 'Treatment disposition' and 'Subject status' eCRFs)
- Number (%) of participants who have entered the post-treatment follow-up (based on the 'Treatment disposition' and 'Subject status' eCRFs));
    - Number (%) of participants who have discontinued from the post-treatment follow-up (based on the 'Post-treatment follow-up disposition' eCRF);
    - Reasons for discontinuation from the post-treatment follow-up (based on Post-treatment follow-up disposition' eCRF);

Protocol deviations

All protocol deviations will be listed.

2.3.2 Basic demographic and background data

All demographic data will be summarized and listed for the FAS by treatment group. Categorical data (e.g. race) will be summarized by frequency counts and percentages; the number and percentage of participants with missing data will be provided. Continuous data (e.g. age, weight, etc.) will be summarized by descriptive statistics (N, mean, standard deviation, median, minimum and maximum). BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight at baseline.

2.3.3 Other

All data collected at baseline will be listed as appropriate.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Listings of each component of study treatment with dose reductions, interruptions or permanent discontinuations, and the reasons will be provided by treatment group based on the safety set. Details of the derivations and summaries are provided in the following sections.

2.4.2 Dose reductions, interruptions or permanent discontinuations

Dose administered (mg) and dosing frequency from the "Study Treatment" or "Study Treatment Summary" eCRF of each component of study treatment will be used to determine the dose reductions, titrations and interruptions.

'Dose permanently discontinued' box ticked from the "Study Treatment" or "Study Treatment Summary" eCRF of each component of study treatment will be used to determine permanent discontinuation.

Dose reductions

For alpelisib, a dose reduction is defined as a decrease in dose from the previous non-zero dose to another non-zero dose less than the protocol planned starting dose, even if this decrease has been directly preceded by an interruption. For example, in the sequence 300 mg daily to 0 mg to 250 mg daily, the 250 mg dose will be counted as a reduction. On the other hand, if the dose decrease is followed by an interruption, with the dose resuming at the same level prior to the interruption (e.g. in the sequence 250 mg daily to 0 mg to 250 mg daily), the second dose decrease will not be counted as dose reduction.

If, due to a dosing error, a participant receives a higher than planned starting dose and moves down to the planned starting dose then this is not considered a dose reduction. However if the dose change is from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is considered a dose reduction (e.g. in the sequence: 350 mg daily to 300 mg daily to 250 mg daily; 250 mg is considered a dose reduction).

If, due to a dosing error, a participant receives a lower than previous non-zero dose and resumes later at the protocol specified dose reduction, then the lower dose received due to dosing error

and protocol specified dose reduction are dose reductions (e.g. in the sequence 300 mg daily to 200 mg daily to 250 mg daily, then 200 mg and 250 mg are considered dose reductions).

If, due to a dosing error, a participant receives a lower than previous non-zero dose and resumes later at a lower than previous non-zero dose, then 2 dose reductions will be counted (e.g. in the sequence 300 mg daily to 250 mg daily to 200 mg daily, 250 mg and 200 mg are dose reductions).

For fulvestrant, dapagliflozin and metformin XR, the reduction counting rules from above apply.

Table 2-2 Examples of Dose Reduction for alpelisib

Sequence	Reduction
With dose change	
300 mg daily to 250 mg daily to 0 mg to 250 mg daily	1 reduction (the 1st 250 mg)
300 mg daily to 300 mg daily to 0 mg to 250 mg daily	1 reduction (250 mg)
300 mg daily to 0 mg to 250 mg daily	1 reduction (250 mg)
With interruption	
300 mg daily to 0 mg to 300 mg daily	0 reductions
With dosing error	
300 mg daily to 250 mg daily to 200 mg daily*	2 reductions (250 mg, 200 mg)
300 mg daily to 200 mg daily* to 300 mg daily	1 reduction (200 mg)
300 mg daily to 200 mg daily* to 250 mg daily	2 reductions (200 mg, 250 mg)
300 mg daily to 400 mg daily* to 350 mg daily*	0 reductions since 400 mg and 350 mg are dose escalations not reduction
300 mg daily to 150 mg daily* to 300 mg daily	1 reduction (150 mg)
With dosing error at the 1st administration	
150 mg daily* to 300 mg daily	1 reduction (150 mg)
150 mg daily* to 0 mg to 150 mg daily* to 300 mg daily	1 reduction (150 mg)
150 mg daily* to 300 mg daily to 0 mg to 250 mg daily	2 reductions (150 mg and 250 mg)

*dosing error

Dose interruptions

An interruption is defined as a 0 mg dose on one or more days between two non-zero dosing records. Any two or more consecutive zero doses of alpelisib (e.g. in the sequence 300 mg daily to 0 mg to 0 mg to 300 mg daily) or other study treatment component (fulvestrant, dapagliflozin or metformin XR) will be counted as 1 interruption if the reasons for these two consecutive dose interruption are the same. It will be counted as two different interruptions only if the reasons are different. For participants who have dose interruption checked in the eCRF but

never resume with a non-zero dose, the dose interruption will not be counted. For example, in the sequence of 300 mg daily to 0 mg (dose interruption) to 0 mg (dose permanently discontinued), the 0 mg (dose interruption) will not be counted as a dose interruption.

Note: The last zero dose of any study treatment component at permanent discontinuation is not considered as a dose interruption.

2.5 Analysis supporting primary objective

The primary objective is to determine whether prophylactic dapagliflozin plus metformin XR compared to prophylactic metformin XR alone reduces the occurrence of severe hyperglycemia events over the first eight weeks of alpelisib plus fulvestrant treatment (from Cycle 1 Day 8 to Cycle 3 Day 8).

2.5.1 Primary endpoint

The primary endpoint (variable attribute of the primary estimand; refer to Section 1.2.1) is the occurrence of severe (Grade ≥ 3) hyperglycemia over the first eight weeks of alpelisib plus fulvestrant treatment, defined as any glucose laboratory values > 250 mg/dL (> 13.9 mmol/L) from Cycle 1 Day 8 to Cycle 3 Day 8.

Note: assessments from Cycle 1 Day 5 up to Cycle 3 Day 11 are allowed due to the 3-day visit window (Protocol Section 8).

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis to assess the difference in the percentage of participants with severe hyperglycemia between the two treatment arms will not be conducted.

The occurrence of severe hyperglycemia from Cycle 1 Day 8 to Cycle 3 Day 8 documented after the initiation of additional antihyperglycemic therapies will be counted for the primary endpoint summary (refer to Section 1.2.1 for more information on primary estimand).

The primary endpoint will be summarized based on the Safety Set according to the treatment participants actually received. The percentage of participants with severe hyperglycemia per treatment arm will be summarized without confidence intervals.

2.5.3 Handling of intercurrent events

The primary estimand will account for different intercurrent events as explained in the following:

1. **Discontinuation of alpelisib or not receiving any alpelisib:** occurrence of severe hyperglycemia events collected after discontinuation of alpelisib or without any exposure to alpelisib will be used for the primary endpoint summary (treatment policy strategy)
2. **Discontinuation and/or interruption of prophylactic antihyperglycemic therapies:** occurrence of severe hyperglycemia events collected after discontinuation and/or interruption of prophylactic antihyperglycemic therapies will be used for the primary endpoint summary (treatment policy strategy)

3. **Dose interruption and/or reduction of alpelisib:** occurrence of severe hyperglycemia events collected after dose interruption and/or reduction of alpelisib will be used for the primary endpoint summary (treatment policy strategy)

2.5.4 Handling of missing values not related to intercurrent event

Missing data will not be imputed.

2.5.5 Sensitivity analyses

Not applicable.

2.5.6 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

The secondary objectives are to compare the two treatment groups with respect to PFS, and to evaluate the overall response rate (ORR) and clinical benefit rate (CBR). The analyses will be based on FAS and will include all data observed up-to the cut-off date.

No inferential testing is planned for secondary endpoints.

2.6.1 Secondary endpoints

2.6.1.1 Progression-free survival (PFS)

PFS will not be analyzed due to the permanent halt of recruitment and early termination of study.

Overall response rate (ORR)

ORR with confirmed response is defined as the proportion of participants with BOR of confirmed complete response (CR) or confirmed partial response (PR), as per local review and according to RECIST 1.1 (see Section 16.4 of the study protocol) and Section 5.4.2 of this document.

ORR with confirmed response will be calculated based on the FAS. Participants with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional anti-neoplastic therapy or surgery) and within 30 days after the last administration of study treatment will be considered in the assessment of best overall response.

Further anti-neoplastic therapies will be identified from the data collected on the "Concomitant Antineoplastic Therapy" eCRFs with indication "Breast Cancer". Palliative radiotherapy is the only setting of radiotherapy allowed during the study. Therefore, palliative radiotherapy will not be considered as an anti-neoplastic therapy for assessment of BOR. Continuation of combination partner therapy alone after end of study treatment will also not be considered as a new anti-neoplastic therapy.

Clinical benefit rate (CBR)

CBR with confirmed response is defined as the proportion of participants with a best overall response of confirmed complete response (CR) or confirmed partial response (PR), or an overall response of stable disease (SD) lasting for at least 24 weeks. CR, PR, and SD are defined as per local review according to RECIST 1.1 (see Section 16.4 of the study protocol). A participant will be considered to have SD for 24 weeks or longer if a SD response is recorded at 24-1=23 weeks or later from randomization, allowing for the ±1 week visit window for tumor assessments. Participants with only non-measurable disease at baseline will be included in the numerator only if they achieve a complete response or have a 'Non-CR/Non-PD' response at 24-1=23 weeks or later from randomization.

ECOG performance status

The ECOG PS scale (Table 2-3) will be used to assess physical health of participants, ranging from 0 (most active) to 5 (least active):

Table 2-3 ECOG Performance Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

The intervals in Table 2-4 will be used to group the ECOG PS data over time. Day in columns 2 and 3 is defined as date of ECOG PS assessment date – randomization date + 1. The correspondence with Day in column 1 assumes that a participant is treated on the day of randomization; however the definition of Day in columns 2 and 3 still applies if this is not the case, i.e. randomization date is taken as the reference for the windows.

Table 2-4 Time windows for ECOG PS assessments

Assessment	Target day of assessment	Time Interval
Baseline		≤Day 1
Cycle 2 Day 1	29	Day 2 to day 42
Cycle 3 Day 1	57	Day 43 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle k Day 1 (k≥5)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the worst of the 2 assessments will be used.

2.6.2 Statistical hypothesis, model, and method of analysis

PFS

PFS will not be analyzed due to the permanent halt of recruitment and early termination of study.

ORR/CBR

Overall responses data will be listed.

ECOG performance status

ECOG data will be listed by treatment group and assessment time point.

2.7 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for deaths including on treatment and post treatment deaths will be provided.

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study treatment
2. On-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment
3. Post-treatment period: starting at day 31 after last dose of study treatment.

2.7.1 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged. All information obtained on adverse events will be displayed by treatment group.

The number (and percentage) of participants with treatment emergent adverse events will be summarized by treatment, system organ class, preferred term and maximum severity. A participant with multiple grades for an AE will be summarized under the maximum grade recorded for the event. AEs with a missing CTCAE grade will be included in the 'All grades' column of the summary tables.

A participant with multiple adverse events within a system organ class is only counted once towards the total of the system organ class.

Separate summaries will be provided for serious adverse events if there are serious adverse events reported.

In AE summaries the system organ class will be presented alphabetically and the preferred terms will be sorted within SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the dapagliflozin plus metformin XR treatment group.

The frequency of grade 3 and above AEs will be summarized separately.

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed by treatment group and those collected during the pre-treatment and post-treatment period will be flagged.

2.7.2 Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables adverse events which are not serious adverse events and serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.3 Deaths

All deaths will be listed, post treatment deaths will be flagged.

2.7.4 Laboratory data

Regarding laboratory assessments, data from all sources (central and local laboratories) will be combined. Listing of participants with CTC grade 3 or 4 laboratory abnormalities will be provided.

Liver function parameters

Liver function parameters of interest in this study are total bilirubin (TBIL), ALT, AST and alkaline phosphatase (ALP).

The participants meeting the following categorical liver function test criteria will be listed:

- ALT > 3xULN, 5xULN, 10xULN, 20xULN
- AST > 3xULN, 5xULN, 10xULN, 20xULN
- ALP > 1.5xULN
- ALT or AST > 3xULN, 5xULN, 8xULN, 10xULN, 20xULN
- TBIL > 2xULN, 3xULN

For the following combined categories (the assessments need not be concurrent, i.e. participants are counted based on their most extreme value for each parameter. Further medical review can assess potential confounding factors such as, liver metastases, liver function at baseline etc.

- If AST and ALT ≤ ULN at baseline
  - ALT or AST >3x ULN & TBIL>2x ULN
  - ALT or AST >3x ULN & TBIL>2x ULN & ALP ⩾2x ULN
  - ALT or AST >3x ULN & TBIL>2x ULN & ALP <2x ULN
- If AST and ALT > ULN at baseline
  - Elevated ALT or AST (>3x Baseline value or 8x ULN) & TBIL (>2x Baseline value and 2x ULN)
  - Elevated ALT or AST (>3x Baseline value or 8x ULN) & TBIL(>2x Baseline value and 2x ULN) & ALP ≥2x ULN
  - Elevated ALT or AST (>3x Baseline value or 8x ULN) & TBIL(>2x Baseline value and 2x ULN) & ALP <2x ULN

Additional categories may be added to the above list based on any updates to the internal guidelines on collection, analysis, and presentation of liver safety data.

2.7.5 Other safety data

2.7.5.1 ECG

A listing of participants with notable ECG values will be listed by treatment group as defined in Table 2-5. Notable elevations include only newly occurring ECG. A newly occurring ECG abnormality is defined as an abnormal post-baseline ECG finding that is not present at Baseline.

Table 2-5 Clinically notable ECG values

ECG parameter (unit)	Clinically notable criteria
QT, QTcF (ms)	New > 450 and ≤ 480
	New > 480 and ≤ 500
	New > 500
	Increase from Baseline > 30 to ≤ 60
	Increase from Baseline > 60
PR duration (ms)	Increase from baseline >25% and to a value > 200
	New > 200
QRS duration (ms)	Increase from baseline >25% and to a value > 120
	New > 120
Heart Rate (bpm)	< 50 and decrease from Baseline of > 25%

	> 100 and increase from Baseline of > 25%

2.7.5.2 Cardiac imaging

A listing of participants with newly occurring clinically significant abnormality will be produced by treatment group.

2.7.5.3 Vital signs

Vital signs assessments are performed in order to characterize basic body function. The parameters expected to be collected include: weight, body temperature, pulse rate, and systolic and diastolic blood pressure.

The criteria for clinically notable abnormalities are defined in Table 2-6 below.

Table 2-6 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Systolic blood pressure (mmHg)	≥180 with increase from baseline of ≥20	≤90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤50 with decrease from baseline of > 25%
Body temperature	≥ 39.1	-
Weight (kg)	increase ≥ 10% from Baseline	decrease ≥ 10% from Baseline

Participants with clinically notable vital sign abnormalities will be listed by treatment group. In the listing, the clinically notable values will be flagged and also assessments collected later than 30 days after the last treatment date will be flagged.

2.7.5.4 Other

Data with notable values from other tests will be listed as appropriate.

All assessments collected later than 30 days after the last treatment date will be flagged in the listings.

2.8.2 Duration of follow-up

Study follow-up will be summarized using the following methods:

- Summary of duration between randomization and cut-off date, which are defined as follows:
  - Randomization (recruitment) period = (Date of last participant randomized - Date of first participant randomized + 1) / 30.4375 (months)
  - Duration between randomization and data cut-off date = (Cut-off date – Date of randomization + 1) / 30.4375 (months). This item will be summarized overall.

All summaries will be reported in months.

2.9 Interim analysis

No formal interim efficacy analysis is planned.

3 Sample size calculation

3.1 Primary endpoint(s)

The sample size calculation is based on the primary endpoint occurrence of severe hyperglycemia. The hypotheses to be tested and details of the testing strategy are described in Section 2.5.2.

The incidence of severe hyperglycemia adverse events over the first eight weeks of alpelisib plus fulvestrant treatment in the study treatment arm B (i.e. prophylactic metformin XR alone) is assumed to be 40% based on data from the SOLAR-1 study in HR-positive, HER2-negative, advanced breast cancer participants with a PIK3CA mutation treated with alpelisib plus fulvestrant.

It is expected that treatment with prophylactic dapagliflozin plus metformin XR will result in a 20% reduction in the incidence rate. Approximately 124 participants (62 in each arm) will be required to detect a 20% difference in incidence rate with 80% power using the difference of proportion test at a one-sided 5% level of significance (Table 3-1). Assuming a 5% dropout rate (participants without adequate assessment of glucose laboratory values per protocol from Cycle 1 Day 8 to Cycle 3 Day 8) at the time of primary analysis, approximately 132 participants will need to be randomized to the two treatment arms in a 1:1 fashion.

Table 3-1 Sensitivity of power to changes in assumptions for N=124

Expected reduction in incidence rate	Observed reduction in incidence rate	Power
20%	30%	99.2%
	25%	93.8%
	20%	**79.1%**
	15%	56.1%
	10%	32.0%
	5%	14.2%

Note: Simulations are performed in East 6.4 with number of simulations = 100,000 and randomization seed = 2020.

4 Change to protocol specified analyses

Due to the permanent halt of recruitment and early termination of study, the primary analysis will not be conducted. Instead,

- the primary endpoint will only be summarized descriptively without any supplementary analysis.
- the secondary efficacy endpoint, PFS will only be listed without summaries.
- the secondary efficacy endpoints ORR and CBR will only be listed without summaries.
- there will be no subgroup analyses for efficacy and safety endpoints
- the study treatment such as exposure and dose intensity will only be listed without summaries.
- for safety endpoints, only adverse events, deaths and serious adverse events will be summarized. Other safety endpoints will only be listed for participants with notable values.

5 Appendix

5.1 Imputation rules

The missing or partial date imputation rules will be described in the programming datasets specification document.

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death.

If CTCAE grading does not exist for an adverse event, grades 1 – 5 corresponding to the severity of mild, moderate, severe, life-threatening and fatal will be used. Information on deaths will also be collected on the ‘Death’ eCRF.

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version v4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters shown below.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable for laboratory values. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values will be set equal to X-0.0001 or X+0.0001, respectively

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010) **Page 1**

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9/L	< 3.0 – 2.0 x 10^9/L	< 2.0 – 1.0 x 10^9/L	< 1.0 x 10^9/L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9/L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9/L	< 2.0 - 1.5 x 10^9/L	< 1.5 - 1.0 x 10^9/L	< 1.0 - 0.5 x 10^9/L	< 0.5 x 10^9/L
Lymphocytes [3]↓	10^9/L	LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L	< 0.8 - 0.5 x 10^9/L	< 0.5 - 0.2 x 10^9/L	< 0.2 x 10^9/L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9/L	> 20 x 10^9/L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol/L** or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB - CTC grades in Novartis Oncology (26Oct15)

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010) **Page 2**

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [2] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [2]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[2]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [4]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.
(2) = **Life-threatening consequences and/or hospitalization are not considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.
(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9 /L (lymphocytes) and ≥ 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**
(4) = For Creatinine and Fibrinogen, the **comparison with baseline is not considered** for derivation of LAB CTC grades

LAB - CTC grades in Novartis Oncology (26Oct15)

5.4 Implementation of RECIST

Response and progression evaluation will be performed according to Novartis RECIST guideline (as described in detail in Section 16.4 of the study protocol), which is based on RECIST version 1.1 (Eisenhauer et al 2009). The text below gives instructions and rules to provide details needed for programming.

5.4.1 Overall lesions response for participants with only non-measurable lesions at baseline

Participants without measurable disease per RECIST 1.1 are eligible to enter the study if they have at least one predominantly lytic bone lesion. For participants with non-measurable lesions only at baseline, the overall lesion response will be based solely on non-target lesion response or an occurrence of a new lesion. Non-measurable lesions will be entered as non-target lesions. Therefore, the best overall response is determined from non-target lesion response and presence of new lesions (refer to Table 16-8 in Section 16.4.3.2.9 of the study protocol).

5.4.2 Best overall response (BOR)

The best overall tumor response will be assessed as per RECIST 1.1 criteria. The definitions and the details on the derivation are given in Section 16.4 of the study protocol.

Only tumor assessments performed before the start of any antineoplastic therapies (i.e. any additional antineoplastic therapy or surgery) and within 30 days after the last administration of study treatment will be included in the assessment of best overall response.

- New antineoplastic therapies will be identified from the data collected on 'Concomitant Antineoplastic Therapy" eCRFs.
- Palliative radiotherapy is the only setting of radiotherapy allowed during the study. Therefore, palliative radiotherapy will not be considered as an anti-neoplastic therapy for assessment of BOR unless reported on the "Concomitant antineoplastic therapy – Radiotherapy" eCRF. As per RECIST 1.1, it should not be delivered to a target lesion.
- Continuation of study combination partner therapy alone after end of study treatment without confirmed progression, will also not be considered as a new antineoplastic therapy.

The standard definition of a best overall response evaluation of 'stable disease', 'disease progression' or 'unknown' given in the Section 16.4.3.1 of the study protocol will be used for this study. Best overall response with confirmation of response for each participant is determined from the sequence of overall (lesion) responses (as reported by the investigator for local BOR) according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 7 weeks after randomization (and not qualifying for CR or PR).
- Non-CR/non-PD = at least one non-CR/non-PD assessment (or better) > 7 weeks after randomization date (and not qualifying for CR). This applies only for participants with non-measurable disease alone at baseline.
- PD = progression ≤ 17 weeks after randomization (and not qualifying for CR, PR, SD and non-CR/non-PD)
- NE = all other cases (i.e. not qualifying for confirmed CR or PR and without SD or non-CR/non-PD after more than 7 weeks or without progression within the first 17 weeks).

Participants with best overall response "unknown" will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response NE
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early (≤7 weeks after randomization)
- PD too late (>17 weeks after randomization and not qualifying for CR, PR, SD or non-CR/non-PD)

Special (and rare) cases where BOR is unknown due to both early SD and late PD will be classified as "SD too early".

5.4.3 Disease progression

Progressive disease should only be assigned if it is confirmed by an assessment method as per RECIST 1.1 guidelines (e.g. radiologic assessment, photos for skin lesions, etc.). If a new lesion is detected using an objective assessment method other than radiologic assessment, then it should also be entered as a new lesion in the eCRF with the appropriate method. Discontinuation due to disease progression or death due to study indication, without corresponding supportive data in the RECIST CRF (as defined above), will not be considered as progressive disease in the calculation of best overall response and in the analysis of PFS.

5.4.4 Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from 'with' to 'without' contrast use or vice-versa, regardless of the justification for the change), a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in an NE (unknown) overall lesion response based on the Novartis calculation. However, a response from the investigator or the central blinded reviewer that differs from the Novartis calculated NE is acceptable, if a definitive response assessment can be justified based on the available information.

Potential discrepancies between the modality used and overall lesion response (e.g. change in modality but response is different from 'Unknown') will be queried during the data validation process.

5.4.5 Determination of missing adequate assessments

The term 'missing adequate assessment' refers to assessments that are not done or for which the overall lesion response is 'Unknown'. 'Missing adequate assessment' will also be referred to as 'missing assessment'.

As detailed in Section 16.4.3.2.10 of the study protocol, PFS censoring and event date options depend on the presence and the number of missing tumor assessments.

An exact rule to determine whether there are no, one or two missing TAs is therefore needed. This rule is based on the interval between the last adequate tumor assessment (LATA) date and the event date. The scheduled date of tumor assessments (in weeks from randomization), protocol specified window for tumor assessments, and the thresholds for LATA that belong to a visit can be found in the following table.

Table 5-2 Schedule for tumor assessment and time windows

Assessment schedule		Scheduled date – 1 week	Scheduled date (weeks from randomization)	Scheduled date +1 week	Threshold (weeks)*
Every 8 weeks	Baseline	0	0^	1	n/a
	C3D1	7	8	9	12

for the first 12 months	C5D1	15	16	17	20
	C7D1	23	24	25	28
	C9D1	31	32	33	36
	C11D1	39	40	41	44
* The mid-point between current and next visit (except for baseline) and the upper limit for LATA to be matched to a certain scheduled assessment, e.g. if LATA is at week 13, this is after threshold for C3D1 and before that for C5D1, so the matching scheduled assessment is C5D1. ^ Day of randomization is taken as 0.					

To calculate the number of missing tumor assessments, the LATA before an event is matched with a scheduled tumor assessment using the time window in Table 5-2 (essentially whichever scheduled assessment it is closest to). Two thresholds, D1 and D2 are calculated for that scheduled assessment based on the protocol-specified schedule and windows

- An event after LATA+D1 will be considered as having >=1 missing assessment
- An event after LATA+D2 will be considered as having >=2 missing assessment

The threshold is calculated as D1 = 8 + 2 = 10 weeks and D2 = 2*8 + 2 = 18 weeks for that scheduled assessment based on the protocol-specified schedule and windows.

Therefore, using the D2 definition above, the censoring of an event occurring after ≥2 missing TAs can be refined as follows: if the distance between the last adequate TA date and the PFS event date is larger than D2, then the participant will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments.

The same definition of D2 will be used to determine the PFS censoring reason. If the distance between the last adequate tumor assessment date and the earliest of the following dates (analysis cut off, consent withdrawal etc.) is less than or equal to D2:

- Analysis cut-off date
- Date of consent withdrawal
- Date of loss to follow-up

then the censoring reason will be 1. 'Ongoing without event', 2. 'Withdrew consent' or 3. 'Lost to follow-up', respectively. However, if this distance is larger than D2 with no event observed, then the censoring reason will be 'Adequate assessment no longer available'.

No baseline tumor assessments

For the PFS analysis, as specified in Table 16-9 in Section 16.4.3.2.10 of the study protocol, since the timing of disease progression cannot be determined for participants with missing baseline tumor assessment, these participants are censored in the PFS analysis at the date of randomization. This rule however only applies to the disease progression component of the PFS assessment, and not to the survival component. Participants without baseline tumor assessments who die within D1 distance (see Section 5.4.5 for definition) of randomization will be counted as having an event in the derivation of PFS at the date of death.

6 References

- Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer; 45:228-47