STATISTICAL ANALYSIS PLAN

Study Protocol Number:	H3B-6545-A001-101
Study Protocol Title:	A Phase 1-2 multicenter, open label trial of H3B-6545, a covalent antagonist of estrogen receptor alpha, in women with locally advanced or metastatic estrogen receptor-positive, HER2 negative breast cancer
Date:	15 Mar 2023
Version:	Version 3.0

REVISION HISTORY

Revisions to Version 2.0
Date: 15 Mar 2023

CCI

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADI	actual dose intensity
AE	adverse event
AF	allelic frequency
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	AUC from zero time extrapolated to infinite time
$AUC_{(0\text{-}t)}$	AUC from zero time to time of last quantifiable concentration
BP	blood pressure
BSAP	bone-specific alkaline phosphatase
CxDx	cycle (CxDx = Cycle x Day x)
cfDNA	cell-free DNA
CL/F	apparent total clearance following oral administration
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal cross-linking telopeptide of type 1 collagen
DBP	diastolic blood pressure
DCR	disease control rate
DET	double endometrial thickness
DLT	dose-limiting toxicity
DOR	duration of response

Abbreviation	Term
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOT	end of treatment
ER	estrogen receptor
ERα	estrogen receptor alpha
ESR1	estrogen receptor 1 gene
HR	heart rate
FAS	full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)/disease progression
PFS	progression-free survival
PG	pharmacogenetic(s)
PgR	progesterone receptor
PINP	amino-terminal propeptide of type 1 collagen
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	preferred term
Q1, Q3	first quartile, third quartile
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
R_{ac}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
RES	response evaluable set
RR	respiratory rate

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System
SBP	systolic blood pressure
SD	stable disease
SI	Système International
SOC	system organ class
SSC	Study Steering Committee
StD	standard deviation
TEAE	treatment-emergent adverse event
t_{max}	time at which the highest drug concentration occurs
ULN	upper limit of normal
V_Z/F	apparent volume of distribution at terminal phase
WBC	white blood cell/white blood cell count
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol H3B-6545-A001-101, Amendment 09, dated 29 August 2022: A Phase 1-2 multicenter, open-label trial of H3B-6545, a covalent antagonist of estrogen receptor alpha, in women with locally advanced or metastatic estrogen receptor-positive, HER2 negative breast cancer.

3.1 Study Objectives

3.1.1 Phase 1 Primary Objective

The primary objective of the Phase 1 portion of this study is to:

- Determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of H3B-6545 in women with locally advanced or metastatic estrogen receptor-positive, HER2-negative breast cancer.

3.1.2 Phase 1 Secondary Objectives

The secondary objectives of the Phase 1 portion of this study are to:

- Evaluate the safety and tolerability of H3B-6545 as a single agent administered orally (PO) once daily (QD) over a 28-day cycle in this subject population.
- Characterize the plasma pharmacokinetics (PK) of H3B-6545.
- Estimate the efficacy of H3B-6545 in terms of response rate, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS).

3.1.3 Phase 1 Exploratory Objectives

The exploratory objectives of the Phase 1 portion of this study are to:

CCI

3.1.4 Phase 2 Primary Objective

The primary objective of the Phase 2 portion of this study is to:

- Estimate the efficacy of H3B-6545 in terms of best overall response rate, DOR, DCR, clinical benefit rate (CBR), PFS, and OS in with (ER)-positive, HER2-negative breast cancer and in those with and without estrogen receptor alpha (ERα) mutation (including a clonal *ESR1* Y537S mutation).

3.1.5 Phase 2 Secondary Objectives

The secondary objectives of the Phase 2 portion of this study are to:

- Further characterize the safety of H3B-6545 in this patient population.
- Further characterize the PK of H3B-6545. At least sparse PK samples will be collected from all patients on study.
- Evaluate the effect of a high-fat meal on the relative bioavailability of H3B-6545.
- Assess the effect of H3B-6545 on serum bone turnover markers, namely bone-specific alkaline phosphatase (BSAP), for osteoclast metabolism; amino-terminal propeptide of type 1 collagen (PINP), for bone formation; and C-terminal cross-linking telopeptide of type 1 collagen (CTX), for bone resorption.
- Assess the effect of H3B-6545 on endometrial thickness and uterine volume. This objective will be assessed in a subgroup of women with intact uteri.

3.1.6 Phase 2 Exploratory Objectives

The exploratory objectives of the Phase 2 portion of this study are to:

CCI

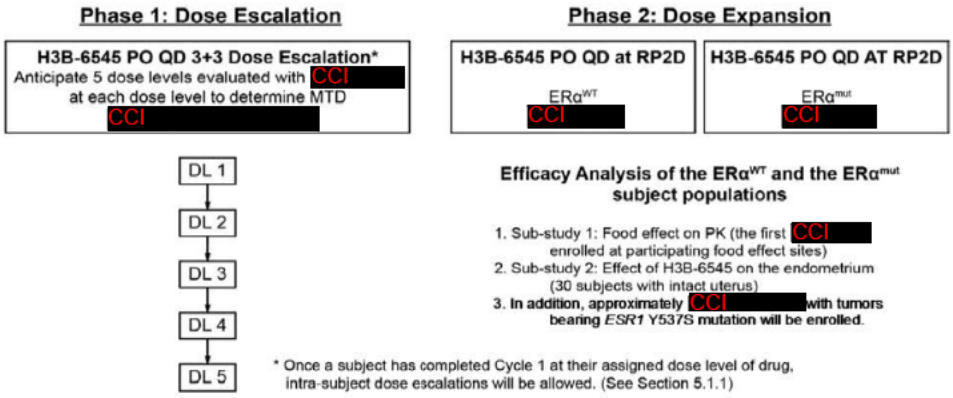
[redacted]

3.2 Overall Study Design and Plan

This is a first-in-human, multi-center, open-label, dose-escalation followed by dose expansion Phase 1/2 study of H3B-6545 for women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer. The study contains a Phase 1 dose escalation part, and a Phase 2 dose expansion portion as shown below:

- The Phase 1 dose escalation part will follow a standard 3+3 cohort design to determine the MTD/RP2D. Once a subject has completed Cycle 3 at her assigned dose level of drug, intra-subject dose escalation will be allowed.

- The Phase 2 dose expansion part will examine the efficacy of the RP2D. Two substudies are included to examine the food effect on PK and effect of H3B-6545 on the endometrium. In addition, approximately CCI subjects having a clonal *ESR1* Y537S mutation, in the absence of *ESR1* D538G mutation are enrolled to examine the efficacy.



Abbreviations: DL=dose level; ERα^mut=estrogen receptor alpha mutant; ERα^WT=estrogen receptor alpha wild-type; MTD=maximum tolerated dose; PK=pharmacokinetics; PO=orally (by mouth); QD=once daily; RP2D=recommended Phase 2 dose.

All subjects entering this study will receive H3B-6545 PO once daily. Efficacy, safety and PK/PD will be assessed according to the Schedule of Assessments (Protocol Appendix E). Subjects are permitted to continue treatment with H3B-6545 until disease progression, unacceptable toxicity, or decision to discontinue treatment by the subject or the study physician. After discontinuation from protocol treatment, subjects must be followed for adverse events (AEs) for 28 days after their last dose of study drug. If a subject discontinues therapy for a reason other than disease progression, they will continue to be evaluated for response until disease progression or until they start a new anti-cancer therapy. Following disease progression, all subjects will be followed for survival at least every 12 weeks, and survival follow-up will end 6 months after the last subject receives their first dose of study treatment (at the time of data cutoff for the primary analysis) (as of Amendment 9), and no survival follow-up will be done in the Extension Phase.

The primary analysis for efficacy will be based on data collected 6 months after the last subject receives their first dose of study treatment.

4 DETERMINATION OF SAMPLE SIZE

4.1 Phase 1

CCI [redacted]

4.2 Phase 2

In the Phase 2 portion of the study, for subjects enrolled prior to Amendment 06, Simon two-stage design (Simon, 1989) will be used in evaluating the response rate in the response evaluable set (RES, defined in Section 5.2.1). Subjects in the Phase 1 part who were treated at the RP2D and were deemed evaluable, will be included in the RES. CCI [redacted]

CCI [redacted]

4.2.1 Sample size calculation for the Phase 2 food-effect sub-study

CCI [redacted]

4.2.2 Sample size calculation for the endometrium sub-study

CCI [redacted]

5 STATISTICAL METHODS

As of CCI [redacted] the RP2D of H3B-6545 has been determined as CCI [redacted]

Three sets of analysis will be performed, including subjects from both Phase 1 and Phase 2 portions of the study, which also includes subjects enrolled under Amendment 06.

Presentation by treatment group: grouping by starting dose levels will be applied to all analyses, unless specified otherwise. The default analysis set is full analysis set (FAS, defined in Section 5.2.1) for all analysis, and response evaluable set (RES, defined in Section 5.2.1) will be applied to selected analysis of response rate.

Presentation by baseline *ESR1* mutation groups: grouping by *ESR1* mutation groups (per sponsor approved laboratory analysis of cfDNA) will be applied to selected efficacy and safety analysis. The default analysis set is FAS subjects who started on CCI [redacted] with known *ESR1* status.

For presentation by baseline *ESR1* mutation groups, the following definitions are used to define the mutation groups per sponsor approved laboratory analysis of cfDNA, only including subjects with known *ESR1* status:

- **Clonal Y537S** consists of all subjects who receive at least 1 dose of study drug, carry *ESR1* Y537S at a mutation AF ≥ 0.5%, and do not carry *ESR1* D538G at an AF ≥0.5%.
- **Clonal D538G** consists of all subjects who receive at least 1 dose of study drug, carry *ESR1* D538G at an AF ≥0.5%, and do not carry *ESR1* Y537S at an AF ≥ 0.5%.
- **Clonal Y537S or clonal D538G** consists of all subjects who are either clonal Y537S or clonal D538G, defined above.
- **Polyclonal Y537S and D538G** consists of all subjects who receive at least 1 dose of study drug and carry both *ESR1* Y537S at an AF ≥0.5% and *ESR1* D538G at an AF ≥0.5%
- **Y537S and D538G negatives** consists of all subjects who receive at least 1 dose of study drug and carry neither *ESR1* Y537S at an AF ≥0.5% nor *ESR1* D538G at an AF ≥0.5%.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (StD), median, the first quartile (Q1), the third quartile (Q3), minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects. In addition, all data will be presented in subject data listings unless otherwise specified.

5.1 Study Endpoints

5.1.1 Phase 1 Primary Endpoint

The primary study endpoint for Phase 1 is the occurrence of dose limiting toxicity (DLT) as a function of the dose of H3B-6545 for determination of the MTD and/or RP2D.

5.1.2 Phase 1 Secondary Endpoints

Secondary study endpoints for Phase 1 are:

- Safety/tolerability: the type and frequency of AEs and serious AEs (SAEs) using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03, as well as changes in clinical laboratory values, vital sign measurements and ECG parameters.
- PK: standard primary PK parameters including, but not limited to, the area under the concentration-time curve from zero time to time of last quantifiable concentration ($AUC_{(0-t)}$), maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), and accumulation ratio (R_{ac}).
- Preliminary efficacy: Response will be determined by the investigator assessments. The following endpoints will be determined:
  - Objective response rate (ORR), defined as the proportion of subjects achieving a best overall response (BOR) of confirmed partial or complete response (PR + CR).
  - Duration of response (DOR), defined as the time from the date of first documented and confirmed CR/PR until the first documentation of disease progression as determined by the investigator or death, whichever comes first.
  - Disease control rate (DCR), defined as the proportion of subjects achieving a best overall response of CR, PR, or stable disease (SD).
  - Progression-free survival (PFS), defined as the time from first dose date to the date of the first documentation of disease progression as determined by the investigator or death (whichever occurs first).
  - Overall survival (OS), defined as the time from first dose date to the date of death (event) or date last known alive or data cutoff date, whichever comes first (censored).

5.1.3 Phase 1 Exploratory Endpoints

Exploratory study endpoints for Phase 1 include:

CCI

5.1.4 Phase 2 Primary Endpoint

The primary study endpoint for Phase 2 is ORR, defined as the proportion of subjects achieving a BOR of confirmed PR + CR.

Response will be determined by the investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Protocol Appendix F). Detailed rules for deriving BOR are provided in Appendix 13.1. Note that BOR of SD has to be achieved at least ≥7 weeks after the first dose. All response of CR and PR must be confirmed by repeated scans ≥4 weeks following the initial achievement of response.

Additional efficacy endpoints (determined by investigator assessment):

- Duration of response (DOR), defined as the time from the date of first documented and confirmed CR/PR until the first documentation of disease progression as determined by the investigator or death, whichever comes first.
- Disease control rate (DCR), defined the proportion of subjects achieving a best overall response of CR, PR, or SD. Note that Non-CR/non-disease progression (PD) will be included for subjects without measurable lesion at baseline (Appendix 13.1).
- Progression-free survival (PFS), defined as the time from first dose date to the date of the first documentation of disease progression as determined by the investigator or death (whichever occurs first).
- Overall survival (OS), defined as the time from first dose date to the date of death (event) or date last known alive or data cutoff date, whichever comes first (censored).
- Clinical benefit rate (CBR): defined as the proportion of subjects with BOR of CR, PR, or durable SD (duration of SD ≥23 weeks). For subjects whose BOR is SD, duration of SD is defined as the time from the date of first dose to the date of the first documentation of disease progression or death, whichever occurs first. Note that for subjects without measurable lesion at baseline, timepoint response of Non-CR/non-PD will be considered as SD for analysis purpose (Appendix 13.1).

5.1.5 Phase 2 Secondary Endpoint(s)

Secondary study endpoints for Phase 2 are:

- Safety/tolerability: same as Phase 1.
- Further characterize PK of H3B-6545.
- Evaluate the effect of a high-fat meal on the relative bioavailability of H3B-6545.
- Endometrial thickness and uterine volume in a subgroup of subjects.
- Effect of H3B-6545 on serum bone turn-over markers, namely BSAP (for osteoclast metabolism), PINP (for bone formation), and CTX (for bone resorption).

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Analyses will be performed using the following analysis sets:

- **Full Analysis Set (FAS)**, which will consist of all subjects who receive at least 1 dose of study drug.
- **FAS with Known *ESR1* Status**, which will consist of all subjects who receive at least 1 dose of study drug and have known *ESR1* status per sponsor approved laboratory analysis of cfDNA. Subjects with unknown *ESR1* status will be excluded. This analysis set will be used for two types of analysis:
  - Analysis by *ESR1* mutation groups: clonal Y537S, clonal D538G, clonal Y537S or clonal D538G, polyclonal Y537S and D538G, Y537S and D538G negatives
  - Analysis by *ESR1* mutation status: mutant versus wild type: *ESR1* mutant group includes any mutation at an AF ≥0.05% (ie, limit of detection); *ESR1* wild type group include any mutation at an AF< 0.05%.
- **Safety Analysis Set**, which will consist of all subjects who receive at least 1 dose of study drug. This will be the analysis set for all safety evaluations except DLT results.
- **Dose Evaluable Set,** which will consist of all subjects who were evaluable for DLT in Cycle 1 of Phase 1, as collected on case report form (CRF) page. This will be the analysis set for DLT results. Note that subjects who do not receive study drug for at least 70% of the planned dose of H3B-6545 during the first cycle (28 calendar days) for reasons not considered to be a DLT by both the investigators and the Sponsor will be replaced; the subjects who are replaced will not be considered evaluable for DLT assessments (Protocol Section 10.11.5).
- **PK Analysis Set**: This analysis set will be derived and reported in a separate PK analysis report.
- **Food-effect Analysis Set**: This analysis set will be derived and reported in a separate PK analysis report.

CCI

- **Response Evaluable Set (RES)**, which will consist of those subjects who receive at least 1 dose of study drug and have measurable disease at baseline and at least 1 post-baseline adequate evaluation. This will be the primary analysis set for efficacy evaluations.
- **Endometrium Safety Evaluable Set**, which will consist of those subjects with intact uteri at baseline, who receive at least 1 dose of study drug and have ultrasound assessments at screening/baseline and three months after starting trial therapy.

- **Bone Turnover Markers Evaluable Set**, which will consist of those subjects who have baseline/screening assessments of bone turnover markers and at least one additional assessment at 6 and/or 12 weeks after starting trial therapy. To be included in this set, subjects must have received trial therapy uninterrupted for at least 14 days prior to 6-week or the 12-week assessment.

5.2.2 Subject Disposition

The number and percentage of subjects enrolled (ie, those who signed informed consent) along with reason for screen failure will be summarized.

The number of subjects in each analysis set will be summarized. The number and percent (based on FAS) of subjects who completed/discontinued treatment will be summarized by treatment groups, along with the primary reason for discontinuation.

5.2.3 Protocol Deviations

All important protocol deviations will be determined prior to database lock and will be agreed upon by a cross-functional team review of individual subject data. The summary table and listing of important protocol deviations will be provided using data in the clinical database.

All important protocol deviations will be listed and summarized descriptively.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for the FAS will be summarized by treatment groups using descriptive statistics. Continuous demographic and baseline variables include age (year), weight (kg) and height (cm); categorical variables include age group (>=18 to <65, >=65) sex (male, female), race (White, Black or African American, Asian [Japanese, Chinese, Other Asian], American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other), Ethnicity (Hispanic or Latino, Not Hispanic or Latino), Eastern Cooperative Oncology Group Performance Status (ECOG PS), measurable disease at baseline, bone disease without measurable lesion at baseline (defined by subjects without measurable disease and with non-target bone lesion presented at baseline).

Disease history will be summarized by treatment group:

- Time from tumor diagnosis to date of the first dose (months)
- Age at diagnosis (years) summarized both descriptively and by categories (<65, >=65)
- Location of primary tumor site
- Tumor staging using TNM classification

Disease characteristics at study entry will be summarized by treatment groups (based on FAS), and baseline *ESR1* mutation groups (based on FAS subjects who started on 450 mg)

- Metastatic sites at baseline

- Mutation status of *ESR1*, *PIK3CA (*phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), *AKT1* (AKT serine/threonine kinase 1) at baseline
- Progesterone Receptor (PgR) status and positivity as percentage of PgR positive cells at baseline.

Previous anti-cancer medications will be summarized by treatment groups (based on FAS) and baseline *ESR1* mutation groups (based on FAS subjects who started on 450 mg):

- Number of previous anti-cancer regimens containing endocrine therapies in locally advanced/ metastatic disease settings
- Number of previous anti-cancer regimens not containing endocrine therapies in locally advanced/ metastatic disease settings
- Therapeutic setting of previous anti-cancer regimens
- Type of previous anti-cancer regimens (endocrine, including fulvestrant, aromatase inhibitor (AI), tamoxifen and other, CDK4/6 inhibitor, chemotherapy, other; CDK4/6i and AI; CDK4/6i and fulvestrant) in locally advanced/ metastatic disease settings

Previous radiotherapy will be summarized by treatment groups (based on FAS):

- Number of subjects having prior radiotherapy
- Last radiotherapy site
- Tumor lesion at the site progressed since last radiotherapy
- Time (in month) from end of last previous radiotherapy to first dose of study drug

Listings of demographics, baseline characteristics, disease history and characteristics, previous anti-cancer medications and previous radiotherapy will be provided.

Medical history and current medical condition:

Medical history and current medical condition, as recorded on the CRF, will be listed. Reported medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or later.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the current version of the World Health Organization Drug Dictionary (WHO DD).

Prior medications will be defined as medications that started before the first dose of study drug. Concomitant medications will be defined as medications taken during the treatment period (defined as the period from first dose date to 28 days after last dose date).

Note that a medication can be categorized into multiple categories: it can be prior only, concomitant only, or combination of prior and concomitant.

The number (percentage) of subjects who took prior and concomitant medications will be summarized on the FAS by treatment groups, and by Anatomical Therapeutic Chemical (ATC) class (level 1 and level 3), as well as WHO DD preferred term (PT). All medications will be presented in subject data listings.

In addition, non-pharmacological procedures and palliative radiotherapy will be listed.

5.2.6 Treatment Compliance

No analysis is planned.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

Not applicable.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Examination of Subgroups

Per study design, efficacy endpoints will be evaluated by *ESR1* mutation status (mutant, wild type) defined in Analysis Subsets (Section 5.2.1) for subjects who started on 450 mg. Exploratory subgroup analysis will be performed by:

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Subjects drop out and unevaluable for DLT evaluation would be replaced per protocol.

No imputation for missing data will be performed in general, unless it is indicated for specific considerations. The imputation rules for partial date in order to derive a variable for disease characteristics will be specified in the study analysis dataset specification. For incomplete dates involving efficacy and safety data such as adverse events, concomitant

medications, laboratory values, vital signs and ECGs, a conservative imputation will be used for calculation. The imputation rules will be specified in study analysis dataset specification with more details. For endpoints that determine the percentage of responders, subjects with unknown response will be treated as non-responders.

5.3.6 Other Considerations

Not applicable.

5.4 Efficacy Analyses

Tumors are evaluated every two cycles (8 weeks) by investigator's assessment based on RECIST 1.1. Assessments will continue until disease progression or initiation of new anti-cancer therapy. Detailed BOR derivation rule is included in Appendix 13.1. Detailed PFS censoring is included in Appendix 13.2.

All efficacy parameters will be summarized for the either RES or FAS, or both.

5.4.1 Primary Efficacy Analyses

Primary efficacy analysis will be performed for the primary endpoint ORR:

For ORR:

For testing purposes: two protocol specified hypotheses will be tested separately for subjects dosed prior to Amendment 6 and under/after Amendment 6:

For estimating purposes, ORR will be provided for RES and FAS (regardless of when subjects are dosed), presented by treatment groups, by *ESR1* mutation groups, or by PgR status. The detailed list of ORR analysis is included in Table 1:

Table 1 List of ORR analyses

Purpose	Analysis set	Presentation (grouping)
Protocol defined Hypothesis testing	CCI subjects of RES CCI	Single group
Protocol defined supportive for testing	RES dosed prior to Amendment 6	Treatment groups
Protocol defined Hypothesis testing	RES dosed under/after Amendment 6	Single group
Protocol defined	FAS	Treatment groups
Protocol defined	RES	Treatment groups
Protocol defined subgroup	FAS CCI	*ESR1* status (Mutant, Wild type)
CCI		

ESR1 = estrogen receptor 1 gene, FAS = Full Analysis Set, PgR = progesterone receptor, RES = Response Evaluable Set.

A listing of efficacy data will be provided for FAS, at least including RES flag, starting dose level and date, *ESR1* mutation status and PgR status.

5.4.2 Additional Efficacy Analyses

Additional efficacy analyses will be performed for DCR, CBR, PFS, DOR and OS.

For DCR: estimated DCR and the corresponding Clopper-Pearson 2-sided 95% CI will be presented. The presentation strategy will be similar to the ORR analysis.

For CBR: estimated CBR and the corresponding Clopper-Pearson 2-sided 95% CI will be presented. The presentation strategy will be similar to the ORR analysis.

For PFS: The main analysis of PFS will follow the FDA censoring rule guidance: progression date is assigned to the earliest date when any RECIST 1.1-defined disease progression is

observed without missing more than one adequate radiologic assessments. Details are included in Appendix 13.2.

The distribution of PFS will be estimated using Kaplan-Meier methodology. Median PFS and the corresponding 2-sided 95% CIs will be summarized by treatment groups, *ESR1* mutation groups, or PgR status. The PFS rate at 3, 6, 9, and 12 months will be estimated using the Kaplan-Meier Method and the corresponding 2-sided 95% CIs will be summarized. In addition, Kaplan-Meier plots of PFS will be presented.

In addition to the main PFS analysis, supportive analysis may be performed (specified in Appendix 13.2): 1) considering new anticancer therapy as events, 2) allowing subjects to have events after COVID-19 related censoring, 3) considering clinical PD as events.

A complete list of PFS analysis is included in Table 2:

Table 2 List of PFS analyses

Purpose	Analysis set	Presentation grouping [Table, Figure]
Protocol defined	FAS	Treatment groups [TF]
Protocol defined subgroup	FAS CCI	*ESR1* status (Mutant, Wild type) [T]
CCI		

Sensitivity analysis is not included in the table and will be detailed in TLG shells.

ESR1 = estrogen receptor, F = figure, FAS = Full Analysis Set, G = graph, PFS = progression-free survival, PgR = progesterone receptor, T = table.

For DOR, the analysis will include subjects with confirmed responses. The same logics in censoring rules as those for primary analysis of PFS will be applied. If there are ≥7 subjects with confirmed responses, the median of DOR will be estimated using Kaplan-Meier methodology; median DOR and the corresponding 2-sided 95% CI will be presented by treatment groups on RES. If there are <7 subjects with confirmed responses, DOR will be listed.

For OS, the distribution of OS will be estimated using Kaplan-Meier methodology. Median survival time and the corresponding 95% CI, survival rates at 6, 12, 18, 24, 30 and 36 months, and corresponding 95% CIs will be estimated using Kaplan-Meier method. The analysis will be presented by treatment groups, *ESR1* mutation groups, and PgR status.

In addition, waterfall plot of best percentage change may be provided for RES subjects started on the 450 mg dose and color-coded by *ESR1* mutation groups.

5.4.3 Subgroup Analyses

Efficacy analysis (ORR, CBR, PFS) will be performed using the subgroups defined in Section 5.3.4.

Detailed analyses are provided in Section 5.4.1 and 5.4.2. Additional exploratory subgroup analyses may be performed.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Details of the analysis methods for population PK modeling will not be described in this SAP but will be described in a separate analysis plan.

5.5.1 Pharmacokinetic Analyses

Plasma concentrations of H3B-6545 will be tabulated and summarized by dose level, day, and time.

H3B-6545 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, $AUC_{(0\text{-}t)}$, R_{ac}, and if data permit, area under the concentration-time curve from zero time extrapolated to infinite time ($AUC_{(0\text{-}inf)}$), elimination half-life of H3B-6545 ($t_{½}$), oral clearance (CL/F), and apparent volume of distribution (V_z/F).

The effect of a high-fat meal on AUC and C_{max} of H3B-6545 will be analyzed by their ratios.

All the PK analysis will be included in a separate PK report.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

CCI [redacted]

5.6 Safety Analyses

All safety analysis will be based on the Safety Analysis Set by treatment groups, with the following exceptions: the DLT analysis will be based on the Dose Evaluable Set; the Phase 2 endometrium effects sub-study analysis will be based on the Endometrium Safety Evaluable Set. Subgroup analysis of selected safety data will be performed by *ESR1* mutation groups, or by PgR status.

Safety data will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; numbers and percentages (n [%]) for categorical variables). Safety variables include exposure parameters, treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, Holter ECG results, and endometrium assessment data. Study Day 1 for all safety analyses is defined as the date of the first dose of study drug. Safety summary will include post-baseline data during the treatment period (starting from first dose to last dose + 28 days).

5.6.1 Extent of Exposure

Exposure to study drug H3B-6545 will be summarized descriptively, including the following parameters defined per subject:

- Duration of treatment (in month), defined as (date of last dose – date of first dose +1)/30.4375, regardless of drug interruptions.
- Number of cycles received
- Total dose received (mg)
- Actual Dose Intensity (ADI, mg/day), defined as total dose received (mg)/ duration of treatment (days)

In addition, number of patients with dose reduction and dose interruption will be summarized.

A dose reduction refers to the situation when the administration of H3B-6545 was reduced one level lower. Dose interruptions are identified by 0 doses which are preceded and followed by the same dose level. If the dose after the 0 dose is lower than that before the 0 dose, this dose change will be counted as a dose reduction.

A by-patient listing of the date of study drug administration and the dose administered will be presented. Patients experiencing any dose modification (increase, reduction, or interruption), together with the reasons for dose modification, will also be provided in a separate listing.

5.6.2 Adverse Events

5.6.2.1 Dose Limiting Toxicity Data

In the Dose Evaluable Set, the number (percentage) of patients with DLTs will be presented by starting dose levels for Phase 1 subjects (100 mg, 200 mg, 300 mg, 450 mg and 600 mg).

A listing of patients with DLTs will be provided. Identifiers for AEs associated with each DLT will be noted in the listing.

5.6.2.2 AE Data

Adverse events (AEs) will be collected for each subject until 28 days after last study drug administration. The NCI CTCAE v4.03 will be used for AE reporting.

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events (AEs) will be coded to the MedDRA (version 19.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as:

- An AE that emerged during treatment (from first dose of study drug up to 28 days after last dose), having been absent at pretreatment (Baseline) or
- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state (Baseline), when the AE was continuous.

The AEs will be summarized using the Safety Analysis Set. Only those AEs that were treatment- emergent (TEAE) will be included in summary tables. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A patient will be counted only once within a SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by maximum NCI CTCAE v4.03 grade, and by causal relationship to study drug (Yes [related] and No [not related]).

Number (percent) of subjects will be summarized by treatment groups in the following analysis:

- Overview of TEAEs (including TEAEs, TEAEs by maximum grade, TEAEs by relationship, treatment-emergent SAEs, treatment-related TEAEs, TEAEs leading to study drug discontinuation, TEAEs with Grade ≥ 3, TEAEs leading to study drug reduction, TEAEs leading to study drug interruption, TEAEs leading to death)
- TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum grade
- TEAEs by PT
- TEAEs of Grade ≥3 by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT and maximum grade
- Treatment-related TEAEs of Grade ≥3 by SOC and PT

- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs by SOC, PT and maximum grade
- Treatment related treatment-emergent SAEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs leading to study drug reduction by SOC, PT and maximum grade
- TEAEs leading to study drug interruption by SOC, PT and maximum grade

Summary of death will be provided with number (percent) of subjects who died during study treatment period or after study treatment. Details concerning patients who died will be listed.

In addition, the following patient data listings will be presented:

- Listing of AEs associated with DLT
- Listing of AEs leading to discontinuation from study drug
- Listing of SAEs
- Listing of all AEs

As exploratory subgroup analysis, the following analysis will be performed by *ESR1* mutation groups or by PgR status:

CCI

5.6.2.3 AE of special interest

Hy's law is the only reportable AESI for this protocol and events of Hy's law will be reported and captured in AE summary table (Section 5.6.2.2). Potential Hy's law cases will be listed (Section 5.6.3) and discussed in the clinical study report (CSR).

5.6.2.4 Grouping of AEs

Selected grouped terms will be defined by using coded terms, based on the MedDRA version used at the time of database lock. Grouped AEs will be summarized by treatment groups.

The grouped term "Bradycardia" is defined by PT of "Sinus bradycardia" and "Bradycardia".

5.6.3 Laboratory Values

Laboratory results will be summarized by treatment groups on the safety analysis set. The analysis will include assessment collected at baseline and/or during treatment (from first dose to 28 days after last dose date), using Système International (SI) units, as appropriate. Values that are non-missing and reported as 'below the detectable limit' of an assay will be replaced by half of the detectable limit in the summary tables.

For all quantitative parameters, the numeric value and the change from baseline to each post-baseline visit (including end of treatment visit and safety follow up visit) will be summarized by visit using descriptive statistics. Qualitative parameters summarized by frequencies (number and percentage of subjects) at each post-baseline visit (including end of treatment visit and safety follow up visit) will be reported.

Furthermore, the frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be summarized for selected laboratory parameters, including hemoglobin, White Blood Cell Count (WBC), Absolute neutrophil count (ANC), lymphocytes, platelet count, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, creatinine, estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet in Renal Disease [MDRD] formula), thyroid-stimulating hormone (TSH) and electrolytes. Shift tables will also be produced for selected parameters based on the baseline CTCAE grade and the maximum CTCAE grade at post-baseline visits.

Listings of laboratory results will be provided. In addition, a listing of potential Hy's law cases will be provided, including subjects who meets one of the following criteria at any post-baseline timepoint (not necessarily at the same timepoint): (aspartate aminotransferase or alanine transferase)>3 × upper limit of normal (ULN). Parameters (AST, ALT, Total Bilirubin, ALP as multiples of ULN) at all timepoints will be included. Subjects meeting Hy's Law definition will be discussed in the CSR based on FDA "Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluations, July 2009".

5.6.4 Vital Signs

By-timepoint analysis: descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure [BP], pulse/heart rate [HR], respiratory rate [RR], temperature and weight) during the treatment period and changes from baseline will be summarized by visit, presented by treatment groups on the Safety Analysis Set.

Categorical analysis: the number (percentage) of subjects who meet the criterion (Table 3 and Table 4) with at least 1 post-baseline result during the treatment period will be summarized (based on worst post-baseline results), and presented by treatment groups:

Blood pressure will also be summarized using a shift table from baseline to worst post-baseline by categories defined based on CTCAE grades.

Table 3 Blood Pressure Grades

Grade	Blood Pressure (mm Hg)	
	Systolic	Diastolic
0 (Normal)	≤119	≤79
1 (Prehypertension)	120 – 139	80 – 89
2 (Stage 1 Hypertension)	140 - 159	90 – 99
3 (Stage 2 Hypertension)	≥ 160	≥ 100

For each subject at each visit, systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be graded separately. Then the blood pressure grade will be the worst of the two grades: SBP grade and the DBP grade. The worst blood pressure category per subject during treatment will be used in the shift table.

Table 4 Criteria for Categorical Analysis of Vital Sign Parameters

Parameter	Criteria
Heart rate increase	Changes reflecting a more than 25% increase from baseline to a HR > 100 bpm
Heart rate decrease	Changes reflecting a more than 25% decrease from baseline to a HR < 50 bpm

Bpm = beats per minute, HR = heart rate.

A listing of vital sign measurements will be provided.

5.6.5 Electrocardiograms

5.6.5.1 Continuous 24-hour Holter Data

For Phase 1 subjects, the effects of H3B-6545 on cardiovascular re-polarization will be evaluated via a 12-lead continuous Holter. On Cycle 1, Day 1 and Day 15, monitoring via Holter will begin at least 1 hour prior to dose and continue through at least 24 hours post dose. The analysis of QT intervals corrected using Fridericia's method (QTcF) and other ECG parameters, and exposure-ECG modeling are documented in a separate analysis plan prepared by ERT.

5.6.5.2 Central and Local 12-lead ECG Data

In addition, central triplicate 12-lead ECG are collected at screening, and on Day 1 and Day 15 of Cycle 1 (for Phase 2 subjects), Day 1 of Cycle 2, 3, and 4 (predose and 3 hours postdose), as well as at the End of Treatment (EOT) visit.

Local 12-lead ECG data maybe collected at scheduled visits starting from Cycle 5 until the last cycle prior to the EOT visit, and at unscheduled visits as clinically required.

For each ECG parameter (QTcF, PR, etc), the average of triplicate at each timepoint (screening, predose and post dose on Day 1 of Cycle 1, 2, 3, 4, EOT, unscheduled, etc) will be used in ECG analysis below:

- By-timepoint analysis: ECG parameters numerical results and changes from baseline at each scheduled timepoint (including EOT and safety follow up visit) during the treatment period will be summarized by treatment groups.
- Categorical analysis: the number (percentage) of subjects who meet the following criterion with at least 1 post-baseline ECG result during the treatment period will be summarized (based on worst post-baseline results) and presented by treatment groups:

Table 5 Criteria for Categorical Analysis of ECG Parameters

ECG parameter	Criteria
QTcF	> 450 and ≤ 480 msec
	> 480 and ≤ 500 msec
	> 500 msec
	Change from baseline > 30 and ≤ 60 msec
	Change from baseline > 60 msec
	> 500 msec or change from baseline >60 msec
PR	Change-from-baseline > 25% resulting in PR > 200 msec
QRS	Change-from-baseline > 25% resulting in QRS > 120 msec
HR	Changes reflecting a more than 25% decrease from baseline to a HR < 50 bpm
	Changes reflecting a more than 25% decrease from baseline to a HR < 40 bpm
	Changes reflecting a more than 25% increase from baseline to a HR > 100 bpm

HR = heart rate, QTcF = QT interval corrected for heart rate using Fridericia's formula.

Shift tables will present changes in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) from baseline to worst post-baseline reading; if multiple interpretation records are collected in triplicate on Day 1 predose, the worst interpretation (eg, abnormal is worse than normal) prior to the first dose will be used as baseline interpretation.

All ECG data, including 24 hour continuous Holter ECG, central and local 12-lead ECG data will be listed. All ECG abnormalities based on central/local 12-lead ECG will also be listed.

5.6.6 Other Safety Analyses

5.6.6.1 Endometrium Safety Sub-Study Assessments

For Phase 2 patients in the Endometrium Safety Evaluable Set, summary statistics at each protocol visit for uterine volume and double endometrial thickness (DET) will be displayed.

Change from baseline at all post-baseline assessments will also be presented, including 2-sided 90% confidence interval for change from baseline in DET.

All endometrium assessment data will be listed.

5.6.6.2 Bone Turnover Assessments

For Phase 2 patients in the Bone Turnover Markers Evaluable Set, summary statistics at each protocol visit for BSAP, PINP and CTX will be displayed. Changes from baseline at the 6th week, 12th week and EOT visit will be presented.

All serum bone turnover data will be listed.

5.6.6.3 ECOG PS

ECOG PS will be listed.

5.6.6.4 Other analyses

The following data will be listed:

- Meal questionnaire
- Multiple-gated acquisition (MUGA) or Echocardiogram (Left Ventricular Ejection Fraction, LVEF)
- Pregnancy test

5.7 Other Analyses

The effect of a high-fat meal on H3B-6545 PK is analyzed in a separate document. Other analyses may be conducted as appropriate.

5.8 Exploratory Analyses

Additional exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the CSR.

6 INTERIM ANALYSES

There would be an interim analysis to define the MTD and/or RP2D prior to initiating Phase 2 of the study. There would also be an interim analysis to evaluate the effect of a high-fat meal on H3B-6545 PK. Safety data would be provided and reviewed periodically. Database locks are not required to perform these analyses.

CCI [redacted]

7 CHANGES IN THE PLANNED ANALYSES

Major changes to planned analyses in protocol are summarized below:

Change	Rationale	Sections in SAP
CCI [redacted]	[redacted]	[redacted]
Definition of prior and concomitant medications	New definition allows medications to be classified into multiple categories, reflecting the complete periods of drug administration.	Section 5.2.5

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Baseline is defined as the last non-missing pre-treatment value (or average value for ECG parameters, when multiple assessments are collected in triplicate at a timepoint) from either a scheduled or an unscheduled assessment.

Pre-treatment assessments: if both date and time are available, a pre-treatment assessment is defined as one that is measured before the date and time of the first dose of study drug. If only date is available and time is missing/not collected, scheduled assessment(s) measured on first dose date of study drug will be considered pre-treatment; unscheduled assessment measured on first dose date will be considered as post-treatment.

On treatment assessments (or assessments during treatment period) are defined as post-baseline assessments from first dose date of study drug to 28 days after the last dose of study drug. End of treatment assessments are those collected at the EOT visit. Safety follow up assessments are those collected at the safety follow up visit. On treatment assessments for end of treatment visit and safety follow up visit will be reported in 'by-timepoint' analysis and included in all abnormality/threshold analysis.

Study Day 1 is defined as the date of the first dose of study drug administered.

If there are multiple values reported for an assessment at a specific visit/timepoint, the average value will be calculated and used in summary tables and figures. Both original values and averages will be displayed in subject data listings.

All by-visit analyses will be performed using assessments at corresponding scheduled visits (including EOT and safety follow-up visits). A scheduled visit will be included in summary tables when there are ≥10% subjects (based on number of subjects dosed) having non-missing assessment at the visit. For shift tables, all post-baseline assessments including those collected at scheduled and unscheduled visits will be used.

Further definitions and conventions for data handling will be presented in "Programming Specifications".

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using Statistical Analysis System (SAS) version 9.4 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

SAS Institute Inc. (2002): The SAS System, Version 9.4. Cary, NC. SAS Institute Inc.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404–13.

Morales L, Neven P, Timmerman D, Wildiers H, Lonstantinovic M, Christiaens MR, et al. Prospective assessment of the endometrium in postmenopausal breast cancer patients treated with fulvestrant. Breast Cancer Res Treat. 2009;117:77-81.

Simon R. Optimal two-stage designs for phase 2 clinical trials. Control Clin Trials. 1989;10:1-10.

13 APPENDICES

13.1 General Rules Deriving Best Overall Response

The BOR is determined once all the data for the subject is known. For this study, a confirmation of complete responses or partial responses is required ≥ 4 weeks after the initial assessment of response. In order for SD to be considered the BOR, it must occur ≥7 weeks following the first dose of study drug. For subjects who do not have a target lesion at baseline, a timepoint response of Non-CR/Non-PD will be treated as SD in BOR derivation, and will be included in DCR and CBR calculation.

To program the BOR per RECIST, the rules below will be followed:

1. The tumor response data collected via the CRFs will be used

2. Any further response assessments after the first PD identified will not be considered for the BOR determination, however they will be presented in the data listings

3. Any tumor assessments after the subject starts a new anti-cancer therapy will not be considered

4. If there are 2 or more consecutive missing adequate tumor assessments, all subsequent assessments will not be considered for the determination of BOR.

Note that the duration between 2 adequate tumor assessments, as well as the duration between the last adequate tumor assessment and death or PD, will be used to identify the cases where 2 or more consecutive tumor assessments are missing. Using the start day and the end day to denote the study days of the two endpoints of the duration, duration = end day – start day. If the duration is longer than 16 weeks + 2 × 7 days (tumor assessment window) – 1 day (ie, 125 days), then it is considered that 2 or more consecutive adequate tumor assessments are missing.

Table 6 General Rules Deriving BOR per RECIST 1.1

Timepoint 1 Overall Response	**Timepoint 2 (≥ 4 weeks since Timepoint 1) Overall Response**	**BOR[b]**
CR	CR	CR
CR	PR	SD, PD or PR If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in

		fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
CR	SD/PD	SD if duration of SD ≥ 7 weeks, otherwise PD
CR	NE	SD if duration of SD ≥ 7 weeks, otherwise NE. In a special case, if CR is at the next timepoint after NE, BOR will be CR.
CR[a]		SD if duration of SD ≥ 7 weeks, otherwise NE
PR	CR/PR	PR
PR	SD/PD	SD if duration of SD ≥ 7 weeks, otherwise PD
PR	NE	SD if duration of SD ≥ 7 weeks, otherwise NE. In a special case, if PR or CR is at the next timepoint after NE, BOR will be PR.
PR[a]		SD if duration of SD ≥ 7 weeks, otherwise NE
SD	Any response	SD if duration of SD ≥ 7 weeks, otherwise PD
PD		PD
NE		NE if the subject did not have a post-baseline tumor assessment, or if the subject only had one post-baseline tumor assessment of an early SD (duration < 7 weeks) as the overall response, or post-baseline tumor assessments are not evaluable (ie, recorded as 'NE' as overall responses via the CRF)
UNK		UNK if the subject did not have a baseline tumor assessment

BOR = best overall response, CR = complete response, CRF = case report form, NE = not evaluable, PD = disease progression, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, UNK = unknown.

a: If this was the only tumor response assessment (eg study treatment was discontinued).

b: For subjects who does not have target lesion at baseline, a timepoint response of Non-CR/Non-PD will be treated as SD in BOR derivation.

13.2 PFS Censoring Rules

For the main analysis of PFS, the censoring rules in this SAP and definition of progression date follow the principles of the FDA "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018)". Table 7 below shows the censoring rules for the derivation of PFS.

Table 7 Censoring Rules for the Derivation of PFS in Primary Analysis

No.	Situation	Date of Event (Progression/Death) or Censoring	Outcome
1	No baseline or post-baseline tumor assessments	Date of first dose	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
3	No progression at the time of data cutoff	Date of last adequate radiologic assessment prior to or on date of data cutoff	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Event
6	Death between adequate assessment visits[a]	Date of death	Event
7	Death or progression after more than one missed visit/tumor assessment[b]	Date of last adequate radiologic assessment before missed tumor assessments	Censored

CR = complete response, PD = disease progression, PFS = progression-free survival, PR = partial response, SD = stable disease.
a Adequate tumor assessment is radiological assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators at regular interval as defined in the protocol. Any tumor assessments after new anticancer treatment starts will be removed in the definition of PFS.
b Defined in Appendix 13.1.

The priority of the censoring rules is as follows:

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have a baseline tumor assessment (No. 1), the subject will be censored on the date of first dose. If the subject died within 125 days following first dose and did not receive a new anticancer treatment, it will be counted as an event at the date of death. If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.

- If a subject missed two or more tumor assessments (>125 days) before PD or death (No. 7), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criterion, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4 or No. 7). Supportive analyses will be provided to evaluate robustness of the main analysis:

- Among FAS subjects who started on 450 mg, if more than 15% of subjects are censored due to COVID-19, then a sensitivity analysis will be performed, allowing subjects to have events after COVID-19 related censoring: events or valid assessment after ≥2 consecutive missing assessments (at least 1 due to COVID-19) will be included in PFS derivation, whereas these events and assessment would have been excluded in the main PFS analysis using the FDA censoring rule.
- Among FAS subjects who started on 450 mg, if more than 15% of subjects are censored due to initiation of new anti-cancer therapy, then a sensitivity analysis will be performed: these subjects will be assumed to have events occurred at the censoring date, whereas these subjects will be censored at the censoring date in the main PFS analysis.
- Among FAS subjects who started on 450 mg, if more than 15% of subjects are censored in the main PFS analysis AND discontinued treatment due to clinical disease progression, then a sensitivity analysis will be performed: discontinuation due to clinical disease progression will be considered as a valid assessment of radiological PD, and the FDA censoring rule will be applied to determine the event/censoring status and date.

SIGNATURE PAGE

Author(s):

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I am the author of this document
Signing Time: 03-Mar-2023 | 19:20:47 GMT
80D03A813386429EA1BDAF7EF2657F6F

Date

PPD
PPD
Biostatistics
Eisai, Inc.

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 07-Mar-2023 | 13:18:16 JST
6BAEE0C35BE647EBB3CD148748063E37

Date

PPD
PPD
Clinical Pharmacology Science Department
Eisai Co., Ltd.

Approval(s):

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 03-Mar-2023 | 13:25:57 GMT
C9C18F2AE2C44AE7AC2587487EF5578D

Biostatistics Head of Oncology

Date

PPD
PPD
Eisai, Inc.

DocuSigned by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
Signing Time: 15-Mar-2023 | 11:42:31 GMT
8733E932F3EC44BFB6CC3EC1C32DF48B

Study Director

Date

PPD
PPD
Eisai, Inc.