STATISTICAL ANALYSIS PLAN

Study Protocol Number:	H3B-6545-G000-102
Study Protocol Title:	An Open-Label Multicenter Phase 1b Study of H3B-6545 in Combination with Palbociclib in Women with Advanced or Metastatic Estrogen Receptor-Positive HER2-Negative Breast Cancer
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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 class
AUC	area under the concentration-time curve
$AUC_{(0\text{-}24h)}$	AUC from zero time to 24 hours
$AUC_{(0\text{-}t)}$	AUC from zero time to time of last quantifiable concentration
BOR	best overall response
BP	blood pressure
CI	confidence interval
C	cycle (CxDx = Cycle x Day x)
C_{24}	plasma concentration at 24 hours postdose (nominal sampling time point)
cfDNA	cell-free DNA
CL/F	apparent total clearance following oral administration
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CSR	clinical study report
DCR	disease control rate
DDI	drug-drug interaction
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
FAS	full analysis set
HER	human epidermal growth factor receptor
HR	heart rate
λ_z	terminal phase rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
No.	number
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)/disease progression
PFS	progression-free survival
PG	pharmacogenenomic(s)
PgR	progesterone receptor
PK	pharmacokinetic(s)
PO	*per os*, orally
PR	partial response
PT	preferred term
Q1, Q3	first quartile, third quartile
QD	once daily
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response evaluable set
RP2D	recommended phase 2 dose
RR	respiratory rate

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System
SD	stable disease
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{½}$	terminal elimination phase half-life
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
TLGs	tables, listings, and graphs
WHO	World Health Organization
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-G000-102, version 5.0, Amendment 4.0, dated 29 August 2022.

This is an open-label multicenter Phase 1b study of H3B-6545 in combination with palbociclib in women with advanced or metastatic estrogen receptor-positive (ER+) human epidermal growth factor receptor 2-negative (HER2-) breast cancer.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of H3B-6545 and palbociclib when administered in combination in order to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of this combination in women with advanced or metastatic ER+ HER2– breast cancer.

3.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the pharmacokinetic (PK) profile of H3B-6545 and palbociclib when administered in combination
- To estimate the preliminary clinical activity of H3B-6545 plus palbociclib in terms of objective response rate (ORR), duration of response (DOR), clinical benefit rate (CBR) (defined as complete response [CR], partial response [PR], or stable disease [SD] ≥23 weeks), progression free survival (PFS), and overall survival (OS)

3.1.3 Exploratory Objective

To explore the relationship of blood and tumor biomarkers with clinical endpoints including safety, clinical activity, and PK

3.2 Overall Study Design and Plan

H3B-6545-G000-102 is a multicenter, open-label study of H3B-6545 in combination with palbociclib for women with advanced or metastatic ER+ HER2– breast cancer. This study consists of 2 parts: dose escalation (Part 1) and dose expansion (Part 2). Subjects in dose escalation must have progressed after 2 prior endocrine therapies and may have received up to 1 prior chemotherapy regimen and up to 1 prior CDK4/6 inhibitor. Subjects in dose expansion may have received up to 2 prior endocrine therapies and up to 1 prior chemotherapy regimen, but may not have received a prior CDK4/6 inhibitor in the advanced or metastatic setting.

Treatment cycles will begin with the first dose of palbociclib in Cycle 1 administered orally (PO) once daily (QD) on Days 1 to 21 and H3B-6545 administered PO QD on Days 9 to 28. In all subsequent cycles, palbociclib will be administered on Days 1 to 21 and H3B-6545 will be administered Days 1 to 28. Intrasubject dose escalation is allowed (Section 9.1, Protocol version 5.0, Amendment 4.0). Treatment will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent.

Safety assessments will be collected up to 28 days after last treatment administration, and include adverse events (AEs) (graded by Common Terminology Criteria for Adverse Events [CTCAE] v5.0), laboratory, vital signs, electrocardiogram (ECG) and physical examinations. Tumor assessments will be performed every 8 weeks (± 1 week) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer et al., 2009) and based on investigator assessment, until documented disease progression or starting another anticancer therapy. All subjects will be followed for survival approximately every 3 months, 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 4.0), and no survival follow-up will be done in the Extension Phase. Detailed schedule of procedures and assessments are included in Table 8 of the Protocol (version 5.0, Amendment 4.0).

The data cutoff date for the primary analysis will be approximately 6 months after the last subject of the Dose Escalation Part receives their first dose of study treatment. There will be no subjects enrolled for the Dose Expansion Part.

Dose Escalation Part

A maximum of 4 dose levels are planned, with palbociclib escalated to no higher than 125 mg QD and H3B-6545 escalated to no higher than 450 mg QD (RP2D); see dose escalation in Table 1.

Table 1 Dose Escalation

Dose Level (Cohort)	Palbociclib Dose (mg QD)	H3B-6545 Dose (mg QD)	Number of Subjects
-1	75	300	6
1 (starting dose)	100	300	6
2	125	300	6
3	125	450	6
3b	100	450	6
QD = once daily.			

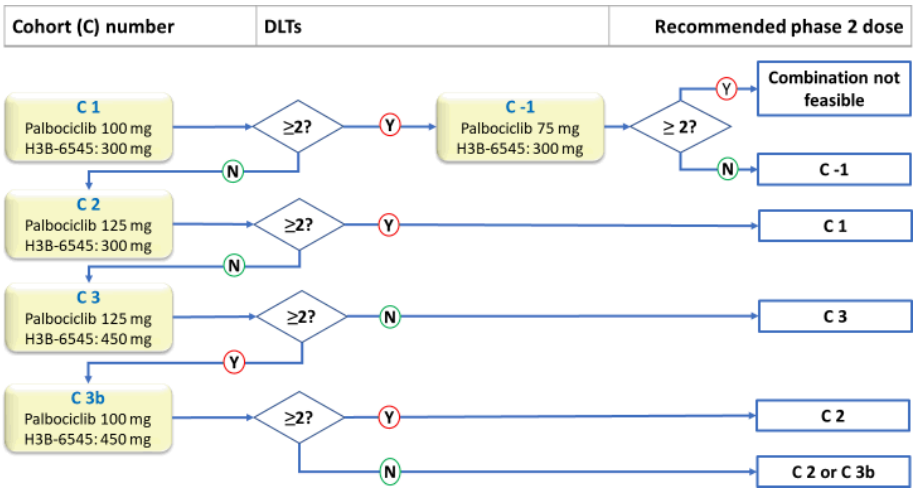
Subjects will be assigned to a dose level in the order of study entry. Dose-limiting toxicities (DLTs) will be assessed during the first 28 days starting from the first day of adding H3B-6545 to palbociclib (Cycle 1 Day 9 to Cycle 2 Day 8) and defined in Table 4 of the Protocol (version 5.0, Amendment 4.0). Subjects not evaluable for DLT assessment will be replaced.

After all subjects in a cohort have completed the DLT observation period, all available safety data will be reviewed by the Safety Review Committee (SRC) consisting of sponsor personnel and investigators, and the decision to proceed to the next dose cohort will be made jointly.

Dose escalation will proceed if <2 of 6 subjects experience a DLT and will continue until a dose level where ≥2 of 6 subjects experience a DLT. If ≥2 of 6 subjects in the starting dose cohort experience a DLT during the first cycle, then the dose level -1 will be explored.

The MTD is defined as the highest dose at which no more than 1 of 6 subjects experiences a DLT in the dose cohort. The RP2D may not exceed the MTD and will be agreed upon by the SRC based on an integrated evaluation of available safety, clinical benefit, PK, and pharmacodynamics (PD) data, for all dose levels tested.

An overview of the study design and the decision rules for selection of the RP2D is presented below.



DLTs = dose-limiting toxicities.

Dose Expansion Part

An additional 12 subjects will be treated at the MTD/RP2D to further characterize safety, tolerability, and PK, and to provide preliminary estimates of efficacy. In Cycle 1, subjects will receive palbociclib PO QD on Days 1 to 21 and H3B-6545 PO QD on Days 9 to 28. In all subsequent cycles, palbociclib will be administered on Days 1 through to 21 and H3B-6545 will be administered Days 1 through to 28.

4 DETERMINATION OF SAMPLE SIZE

Depending on the dose levels to be studied in the dose escalation phase, approximately 12 to 24 subjects may be treated. Dose expansion will enroll 12 additional subjects at the RP2D. Therefore, the study is expected to enroll approximately 24 to 36 subjects. No formal sample size calculation is performed.

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, first quartile [Q1], third quartile [Q3], minimum and maximum. Categorical variables will be summarized as number and percentage of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary study endpoint is to determine the MTD and/or RP2D.

5.1.2 Secondary Endpoints

- AEs and serious adverse events (SAEs), as well as changes in clinical laboratory values, vital sign measurements and ECG parameters
- Standard primaryPK parameters, including, but not limited to, the area under the concentration-time curve from zero time to time of last quantifiable concentration ($AUC_{(0\text{-}t)}$), C_{max}, t_{max}, plasma concentration at 24 hours postdose (nominal sampling time point) (C_{24}), and ratio of the drug-drug interaction (DDI) effect
- ORR, defined as the proportion of subjects achieving a best overall response (BOR) of confirmed partial response or complete response (PR+CR)
- DOR, defined as the time from the date of the first documented and confirmed CR or PR until the first documentation of disease progression (PD) as determined by the investigator or death, whichever comes first. This is only defined for subjects with confirmed responses.
- CBR, defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response, or durable SD (duration is at least 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
- PFS, defined as the time from the first dose date to the date of the first documentation of disease progression as determined by the investigator or death (whichever occurs first)
- OS, defined as the time from first dose date to the date of death from anycause.

5.1.3 Exploratory Endpoint

Not applicable.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

- **Safety Analysis Set**: all subjects who receive at least 1 dose of study drug (either H3B-6545 or palbociclib, or both). This will be the analysis set for all safety evaluations except DLT results.
- **Full Analysis Set (FAS)**: consists of all subjects who receive at least 1 dose of study drug.
- **Dose Evaluable Set**: consists of all subjects who were evaluable for DLT in dose escalation part (Phase 1b). This will be the analysis set for DLT results.
- **Response-Evaluable Set (RES)**: consists of those subjects who receive at least 1 dose of study drug and have measurable disease at baseline and at least 1 adequate post-baseline tumor assessment. This will be the primary analysis set for efficacy evaluations of response rate.
- **Pharmacokinetic Analysis Set**: consists of subjects who received at least 1 dose of study drug and all valid plasma concentrations (at least 3 valid concentrations for noncompartmental analysis).

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 percentage (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.

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 will include age (year), weight (kg) and height (cm); categorical variables will 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),as well as the Eastern Cooperative Oncology Group Performance Status (ECOG PS), measurable disease at baseline, and 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 initial diagnosis to date of the first dose (months)
- Age at diagnosis (years) summarized both descriptively and by categories (<65, ≥65)

Disease characteristics at study entry will be summarized by treatment groups (based on FAS):

- Metastatic sites at baseline
- Mutation status of ESR1, PIK3CA, AKT1 at baseline
- Progesterone Receptor (PgR) status and positivity as percentage of PgR positive cells (per immunohistochemistry [IHC]) at baseline.

Previous anti-cancer medications will be summarized by treatment groups (based on FAS):

- 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, tamoxifen and other, CDK4/6 inhibitor, chemotherapy, other; CDK4/6i and AI; CDK4/6i and fulvestrant) in locally advanced/metastatic disease settings

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 case report form (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 current version of the World Health Organization Drug Dictionary (WHODD).

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.

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

Not applicable.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Subjects that drop out and are 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 AEs, 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 2 cycles (8 weeks) by investigator's assessment based on RECIST 1.1. Assessments will continue until radiological 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 descriptively for either RES or FAS, or both.

5.4.1 Primary Efficacy Analyses

Not applicable.

5.4.2 Secondary Efficacy Analyses

ORR and CBR will be summarized by treatment groups, and exact 95% CIs will be provided using the method of Clopper and Pearson (1934).

In addition, waterfall plot of best percentage change of sum of diameters in target lesion will be provided for RES subjects

PFS analysis 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 1 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 (Brookmeyer and Crowley, 1982) will be summarized by treatment groups. The PFS rate at 3-month, 6-month, and 9-month and 12-month 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.

DOR will be calculated for subjects achieving a best overall response of confirmed PR+CR. 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. The same logics in censoring rules as those for PFS analysis will be applied. If there are <7 subjects with confirmed responses, DOR will be listed.

OS will be censored at the last alive date or data cutoff date, whichever comes first. 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 months, and corresponding 95%CIs will be estimated using Kaplan-Meier method. The analysis will be presented by treatment groups.

5.4.3 Other Efficacy Analyses

Not applicable.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

This section describes statistical analysis for non-compartmental analysis (NCA)-based PK parameters, PD parameters, pharmacogenomic and other biomarkers if applicable. Modeling such as population PK or PK/PD is not included in this SAP and if conducted, will be described in separate analysis plans.

5.5.1 Pharmacokinetic Analyses

Plasma concentrations

The plasma concentrations of palbociclib and H3B-6545 will be summarized using summary statistics (n, mean, standard deviation, median, minimum and maximum) by cohort, day and nominal sampling time points. The following figures will be displayed.

1. Linear and semi-logarithmic plots of mean plasma concentration-time profiles

- The time after dose (nominal time) will be plotted on the X axis and mean plasma concentrations of H3B-6545 and palbociclib will be plotted on the Y axis with standard deviation by cohort and day.

2. Linear and semi-logarithmic plots of individual plasma concentration-time profiles

- The time after dose (actual time) will be plotted on the X axis and individual plasma concentrations of H3B-6545 and palbociclib will be plotted on the Y axis by cohort and day.

PK parameters

The PK parameters of palbociclib and H3B-6545 will include, as applicable, maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), AUC from zero time to time of last quantifiable concentration ($AUC_{(0-t)}$), AUC from zero time to 24 hours ($AUC_{(0-24h)}$), and apparent total clearance following oral administration (CL/F) will be summarized using summary statistics (n, mean, standard deviation, geometric mean [CV%], median, minimum and maximum) by cohort and day. Mean, standard deviation and geometric mean (CV%) are not required for t_{max}. PK parameters will be derived according to Eisai non-compartmental pharmacokinetic Analysis Manual (302-104.01-MNL). To calculate PK parameters, actual sampling time will be used.

The DDI effect will be estimated as a ratio of exposure index (C_{max}, $AUC_{(0-24h)}$, and C_{24}) in the following way in the dose escalation part: ratio of palbociclib exposure on Cycle 1 Day 21/palbociclib exposure on Cycle 1 Day 8 for potential effect of H3B-6545 on palbociclib

and ratio of H3B-6545 exposure on Cycle 1 Day 21/H3B-6545 exposure on Cycle 1 Day 28 for potential effect of palbociclib on H3B-6545. This ratio will be summarized using summary statistics (n, mean, standard deviation, CV%, median, minimum and maximum) by cohort.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The baseline tissue biopsies collected will be used to examine potential baseline markers of response. These markers may include but are not limited to ER, PgR, RB, Ki67, HER2, gene expression and DNA mutations (using standard technologies like quantitative polymerase chain reaction, immunohistochemistry, and other appropriate technology) along with global transcription levels (RNA sequencing).

The whole blood samples will be analyzed for evaluation of cell free DNA (cfDNA) as a source of circulating biomarker (DNA mutations). The samples might be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes, as well as for potential use in companion diagnostic and drug development, and would be reported separately if conducted.

Exposure-response with biomarkers and/or other efficacy endpoints might be explored as appropriate with a population PK model-predicted exposure values and if conducted, will be reported separately.

5.6 Safety Analyses

The determination of the MTD and/or RP2D will be based on Dose Evaluable Set that consists of all DLT-evaluable subjects. Subjects not evaluable for DLT assessment will be replaced.

All other safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; numbers and percentages (n [%]) for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and 12-lead ECG results.

Study Day 1 for all safety analyses is defined as the date of the first dose of study drug (H3B-6545 or Palbociclib, whichever is earlier). Safety summary will include post-baseline data during the treatment period (starting from first dose date of study drug to last dose date of study drug + 28 days).

5.6.1 Extent of Exposure

Exposure will be summarized descriptively by drugs for the Safety Analysis Set, including the following parameters defined per subject:

- Duration of treatment (in months), defined as (date of last dose – date of first dose +1)/30.4375, regardless of drug interruptions.

- Total dose received (mg) by drug (H3B-6545, or palbociclib)
- Actual Dose Intensity (ADI, mg/day) by drug (H3B-6545, or palbociclib): 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 of H3B-6545 or palbociclib (respectively) refers to the situation when the administration of H3B-6545 or palbociclib (respectively) was reduced 1 level lower. For H3B-6545, 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 (eg, increase, reduction, or interruption), together with the reasons for dose modification, will also be provided in a separate listing.

5.6.2 Dose Limiting Toxicity Data

In the Dose-Evaluable Set, the number (percentage) of subjects with DLTs will be presented by treatment groups. A listing of subjects with DLTs will be provided.

5.6.3 Adverse Events

The AEs will be collected for each subject until 28 days after last study drug administration. The NCI CTCAE v5.0 will be used for AE grading.

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. The AEs will be coded to the MedDRA (Version 22.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as the following:

- an AE that emerges during treatment (from first dose of study drug up to 28 days after last dose), having been absent at pretreatment (Baseline) or
- an AE that reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- an AE that worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

The AEs will be summarized using the Safety Analysis Set. Only those AEs that are treatment-emergent 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 subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum CTCAE grade, or by relationship to study drug (Yes

[means related to H3B-6545 or palbociclib or both] and No [means not related to either H3B-6545 or palbociclib]).

Number (percentage) 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, and TEAEs leading to death)
- TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum grade
- TEAEs by PT in decreasing frequency
- 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 (percentage) of subjects who died during study treatment period or after study treatment. Details concerning subjects who died will be listed.

In addition, the following subject 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

5.6.3.1 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". The QT prolongation will be summarized using standard MedDRA query (SMQ).

5.6.4 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 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): AST or ALT >3 x 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 clinical study report based on *FDA Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluations* (2009).

5.6.5 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 (in Table 2 and Table 3) 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:

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

Table 2 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 BP grade will be the worst of the 2 grades: SBP grade and the DBP grade. The worst BP category per subject during treatment will be used in the shift table.

Table 3 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.

5.6.6 Electrocardiograms

Central triplicate 12-lead ECG are collected at Screening, and on Day 1, Day 8, Day 15, Day 21 and Day 28 of Cycle 1, Day 1 of Cycle 2 or above, at the End of Treatment visit, or at the safety follow up visit. Local ECG may also be performed.

For each ECG parameter (QTcF, PR interval, etc), the average of triplicate at each timepoint (screening, predose and postdose at scheduled visits, end of treatment [EOT], unscheduled visits, etc) will be used in ECG analysis below:

- By-timepoint analysis: ECG parameters numerical results and changes from baseline at each scheduled timepoints (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 4):

Table 4 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 interval	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

ECG = electrocardiogram, 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 central and local 12-lead ECG data, will be listed. All ECG abnormalities based on central/local 12-lead ECG will also be listed.

5.6.7 Other Safety Analyses

5.6.7.1 ECOG PS

ECOG PS will be listed.

5.6.7.2 Other analyses

The following data will be listed:

- Multiple-gated acquisition (MUGA) or Echocardiogram (ECHO) for Left Ventricular Ejection Fraction (LVEF)
- Pregnancy test

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

No formal interim analyses are planned. However, the cumulated safety and efficacy data by dose level will be reviewed periodically by the sponsors and investigators. The continuation of study enrollment will depend on the totality of the efficacy and safety data.

7 CHANGES IN THE PLANNED ANALYSES

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

Major changes of the analysis plan between SAP v1.0 to v2.0 are as follows:

- Specified new timing of primary analysis according to Protocol Amendment 04 (29 Aug 2022).
- Clarified summary of previous anti-cancer therapies and subgroup analysis
- Geometric mean (CV%) was deleted from the summary statistics for plasma concentrations of palbociclib and H3B-6545.
- The PK parameters calculated based on the terminal phase rate constant (λ_z) ($t_{½}$ and V_z/F) were deleted from the analysis plan, because the blood sampling time points were not enough to calculate λ_z accurately.
- Definitions and conventions for PK data handling were added.

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.

Pharmacokinetic assessments: The lower limit of quantification (LLOQ) in plasma is 1.00 ng/mL for palbociclib and 1.00 ng/mL for H3B-6545, respectively. While calculating PK parameters, below lower quantification (BLQ) values will be handled according to 302-104.01-MNL. When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.01-MNL. The handling of anomalous concentration values will follow 302-104.01-MNL. When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied for drug concentrations and PK parameters.

Typical variable	Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	Standard deviation	Geometric Mean	CV (%)
Plasma concentration	ng/mL	X	Significant digits	3	3	3	–	–
C_{max}	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}	h	X	Fixed decimal places	2	2	–	–	–
AUC	ng•h/mL	X	Significant digits	3	3	3	3	3
CL/F	L/h	X	Significant digits	3	3	3	3	3
Ratio of exposure index	No units	X	Significant digits	3	3	3	3	3

Individual pharmacokinetic data: The following data will not be included in the calculation of summary statistics.

- Plasma concentration data at predose if the blood samples are collected after administration
- PK data (plasma concentrations and PK parameters) in a patient with any dose modification (increase, reduction, or interruption) within 3 days prior to the blood sampling.

  ie, The following PK data will not be included in the calculation of summary statistics;

  - *PK data of palbociclib from a patient with dose modification in palbociclib from C1D5 to C1D8*
  - *PK data of palbociclib and H3B-6545 from a patient with dose modification in palbociclib or H3B-6545 from C1D18 to C1D21*
  - *PK data of H3B-6545 from a patient with dose modification in H3B-6545 from C1D25 to C1D28*
- Dosing and sampling date/time are missing

The following case will be determined individually:

- Significant deviation from the allowance of PK blood sampling schedule

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 (SAS Insitute, 2002), and Phoenix WinNonlin version 7.0 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings and graphs (TLGs) 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

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13 APPENDICES

13.1 General rules deriving best overall response (BOR)

The best overall response (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 best overall response, it must occur ≥7 weeks following the first dose of study drug. 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, 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; and

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; and

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

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 2 endpoints of the duration, duration = end day – start day. If the duration is longer than 16 weeks +2x7 days (tumor assessment window) – 1 day (ie, 125 days), then it is considered that 2 or more consecutive adequate tumor assessments are missing.

Table 5 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, 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 6 below shows the censoring rules for the derivation of PFS.

Table 6 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 2 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).

SIGNATURE PAGE

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