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Clinical Study Protocol

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
Sponsor:	Eisai Inc. 200 Metro Boulevard Nutley, NJ 07110 USA
Sponsor's Investigational Product Name:	H3B-6545 and palbociclib
Indication:	Advanced or metastatic estrogen receptor–positive HER2-negative breast cancer
Phase:	1b
Approval Date(s):	V1.0 06 Dec 2019 (Original Protocol) V2.0 05 May 2020 (Amendment 1.0) V3.0 10 Jul 2020 (Amendment 2.0) V4.0 15 Jun 2021 (Amendment 3.0) V5.0 29 Aug 2022 (Amendment 4.0)
IND Number:	133282
EudraCT Number:	2019-004622-17
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

Date	Highlights of Major Changes Section/Change
06 December 2019	**Original Protocol**
05 May 2020	**Amendment 1**
	Synopsis and Section 8.3.2 Exclusion Criteria - Clarified that double-barrier contraception is considered acceptable, but not highly effective, method of contraception.
	Synopsis and Section 8.3.3 Definition of Dose-Limiting Toxicities - Added ALT or AST > 3 × ULN, in conjunction with total bilirubin > 2 × ULN in absence of liver metastases at baseline and in absence of clinical or radiological evidence of biliary obstruction.
	Section 8.1 Overall Study Design and Plan - Edited Table 4 hepatic toxicity criteria as follows: Added ALT or AST > 3 × ULN, in conjunction with total bilirubin > 2 × ULN in absence of liver metastases at baseline and in absence of clinical or radiological evidence of biliary obstruction.
	Section 8.6.2.1 Schedule of Procedures / Assessments - Edited Table 8 to include vital sign monitoring in all treatment visits.

Date	Highlights of Major Changes Section/Change
10 July 2020	**Amendment 2**
	Synopsis and Section 8.2, Secondary Objectives Secondary Objectives: Global change of disease control rate (DCR), defined as complete response (CR), partial response (PR), or stable disease into clinical benefit rate (CBR), defined as CR, PR, or stable disease lasting for ≥23 weeks. Rationale: This was done in order to be consistent with the reporting standards of breast cancer trials. - To estimate the preliminary clinical activity of H3B-6545 plus palbociclib in terms of objective response rate (ORR), duration of response (DoR), ~~disease control rate (DCR)~~ **clinical benefit rate (CBR; complete response [CR], partial response [PR], or stable disease ≥23 weeks)**, progression-free survival (PFS), and overall survival (OS)
	Synopsis Clarifications on end of study design language: End of study: The cutoff date for the **main** final analysis will be either 12 **approximately 6** months after enrollment of the last subject in the expansion phase or the end-of- treatment visit date for the last subject in

<table>
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the study, whichever occurs first., respectively. The cutoff date for an updated (final) analysis, including OS, will be approximately 24 months after enrollment of the last subject.
Clarifications on dose-limiting toxicities language:
Dose-limiting toxicities (DLTs) will be assessed during the first 28 days starting from the 1st day of adding H3B-6545 to palbociclib (Cycle 1 Day 9 to Cycle 2 Day 8). Subjects who do not receive at least 75% of the scheduled therapy from Cycle 1 Day 9<s>1</s> to Cycle 2 Day 8, for reasons <s>not considered to be a DLT</s>other than toxicity, will not be considered evaluable for DLT assessment and will be replaced. Disease progression and adverse events (AEs) deemed related to disease progression will not be considered DLTs.
Clarifications on Cohort 3b language:
Cohort 3b: If none or only 1 subject experienced a DLT, doses used in this Cohort <s>will</s> and in Cohort 2 could be considered the RP2D. In this case, the SRC will select between Cohort 2 and Cohort 3b for the expansion phase. If 2 or more subjects experienced a DLT, doses used in Cohort 2 will be considered the RP2D.
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Synopsis and Section 9.1, Overall Study Design and Plan
Clarifications on definition of dose-limiting toxicity in the study design:
DLTs: Unless considered not related to <s>tumor progression</s> study drugs, any of the following criteria will qualify as a DLT:
<table>
<tr><td>Hepatic</td><td>- Grade 3 or 4 bilirubin increase
- ALT or AST <s>></s>≥<s>0</s>8 × ULN
- In absence of liver metastases at baseline and in absence of clinical or radiological evidence of biliary obstruction: ALT or AST >3 × ULN, in conjunction with total bilirubin >2 ×ULN</td></tr>
<tr><td>Biochemistry</td><td>- Grade 4
- Grade 3 lasting more than 7 days, unless considered not clinically significant as per the discretion of the investigator</td></tr>
<tr><td>Any other non-hematologic AE</td><td>- Grade 4
- Grade 3 (except diarrhea, rash, nausea, or vomiting lasting ≤72 hours)
- Any drug-related intolerable Grade 2 toxicity (other than hematological AEs) leading to administration of <75% of the dose during the DLT observation period</td></tr>
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a. Laboratory values that meet criteria listed in this table should be repeated and confirmed within 24 hours of the initial results being reported.
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Synopsis, Section 9.1, Overall Study Design and Plan, and Section 9.4.3, Method of Assigning Subjects to Treatment Groups
Clarification on dose expansion in the study design:
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	Dose expansion: 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, s~~S~~**ubjects will receive palbociclib **PO QD** on Days 1 to 21 ~~PO QD~~ 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.
	Synopsis and Section 9.3.1, Inclusion Criteria Clarifications on inclusion criteria 5. Prior therapy in the advanced or metastatic setting: a. Dose escalation: 2 or more prior hormonal therapies. Subjects may have received up to 1 prior chemotherapy regimen and up to 1 prior CDK4/6 inhibitor. b. Dose expansion: Up to 2 prior endocrine therapies and up to 1 prior chemotherapy regimen but may not have received a prior CDK4/6 inhibitor. Note: If the patient was enrolled within 12 months of the end of adjuvant therapy, the adjuvant therapy will also be counted. **Note: Subjects must have documented progression while on or after the most recent therapy.** 6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 7. Life expectancy >12 weeks**, as per investigator's best assessment, during the Screening phase.**
	Synopsis and Section 9.3.2, Exclusion Criteria Removed criterion for intrauterine hormone releasing system and contraceptive implant. 8.Females of childbearing potential who: • Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following: a Double-barrier contraception (considered acceptable method but not highly effective) b Total abstinence (if it is their preferred and usual lifestyle) c An intrauterine device ~~or intrauterine hormone-releasing system~~ ~~d A contraceptive implant~~ ~~e.~~**d** Have a vasectomized partner with confirmed azoospermia.
	Synopsis, Section 9.3.2, Exclusion Criteria, and Section 9.4.7.2, Prohibited Concomitant Therapies and Drugs Removed proton pump inhibitor (PPI) criterion from exclusion criteria and prohibited concomitant medications Rationale: A drug-drug interaction (DDI) study of H3B-6545 with pantoprazole, a PPI, in healthy post-menopausal women demonstrated that H3B-6545 plasma exposure is similar in the absence or presence of pantoprazole, suggesting that restriction on use of PPI or other acid reducing

	agents could be removed from the exclusion list. The United States (US) Prescribing Information and Summary of Product Characteristics for palbociclib state that under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure. 10. Subject received in the 7 days prior to the administration of study drug or is currently receiving any of the following medications: a. Known strong inducers or inhibitors of CYP3A4 or P-glycoprotein (P-gp). b. Medications that have a narrow therapeutic window and are breast cancer resistance protein (BCRP) substrate. c. Medications that have a known risk to prolong the QT interval or induce Torsades de Pointes. d. ~~Proton pump inhibitors and histamine H2 receptor antagonists.~~ ~~Note: Use of antacids is allowed but should be administered ≥2 hours before or ≥4 hours after H3B-6545. The use of palonosetron for the management of nausea and vomiting is also allowed.~~ ~~e.~~**d.** Medications that have a narrow therapeutic window and are predominantly metabolized through CYP2C8, CYP2C9, CYP2C19, or CYP3A4. ~~f.~~**e.** Herbal preparations/medications; these herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng.
	Synopsis and Section 9.3.2, Exclusion Criteria Added criterion for history of interstitial lung disease and non-infectious pneumonitis. **12. Active interstitial lung disease (ILD) or diagnosis of ILD within the last 12 months**
	Synopsis and Section 9.3.2, Exclusion Criteria Added exclusion criterion for active COVID-19 infection or recent exposure to an individual with COVID-19 **14. Exposure within the last 14 days to an individual with confirmed or probable COVID-19 or symptoms within the last 14 days or any other reason to consider the subject at potential risk for an acute COVID-19 infection.** **Note: Please consider testing for active COVID-19 infection prior to starting trial therapy according to the institution guidelines.**
	Synopsis Clarifications on duration of treatment: Treatment Phase: Subjects will continue to receive study treatment until **radiological** disease progression, development of unacceptable toxicity, or withdrawal of consent. **Treatment beyond radiological progression may be allowed if the subject continues to have clinical benefit as per the principal Investigator after discussion and written approval from the Sponsor.**

	Synopsis and Section 9.4.7.3, Permitted Concomitant Medications Clarifications on concomitant drug/therapy: Permitted Concomitant Medications: ~~The use of~~ **No routine prophylactic antiemetic is required. However, the use of** palonosetron, **prochlorperazine, promethazine, and cyclizine** for ~~the~~ management of nausea and vomiting is allowed ~~according~~. **The use of ondansetron and granisetron is not permitted because of their potential** to ~~standard practice guidelines. Use of antacids is allowed but should be administered ≥2 hours before or ≥4 hours after H3B-6545~~**prolong QT interval**. Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following: • Growth factors: **Prophylactic use of GCSF is not allowed from Cycle 1 Day 9 to Cycle 2 Day 8.** Subjects receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pretreatment doses. Following initiation of study treatment, the use of erythropoietic and granulocyte growth factors in accordance with local practice or ASCO guidelines may be implemented at the discretion of the treating physician.
	Synopsis and Section 9.6.1.3.1, Pharmacokinetic Assessments Clarifications on dose escalation: • On Cycle 1 Day 8, PK blood samples to determine plasma concentrations of palbociclib will be collected at predose a~~nd 1, 2, 4, 6, 8, and 24 hours postdose~~ **(within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.** • On Cycle 1 Day 21, PK blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. • On Cycle 1 Day 28, PK blood samples to determine plasma concentrations of H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. • During the treatment phase, PK blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until end of treatment.
	Synopsis and Section 9.6.1.3.1 Pharmacokinetic Assessments Clarifications on dose expansion: • On Cycle 1 Day 21, PK blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose **(within 1 hour before administration of study drug)** and 1 **(±10 minutes)**, 2 **(±15 minutes)**, 4 **(±20 minutes)**, 6 **(±30 minutes)**, 8 **(±30 minutes)**, and 24

	hours **(±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days**. • **During the treatment phase,** PK blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose ~~prior to~~ **in conjunction with** each tumor assessment, that is, approximately every 8 weeks until progression.
	Synopsis and Section 9.6.1.3.2, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Clarifications on dose escalation and dose expansion: • At baseline (during screening), pretreatment fresh biopsies or archival tumor tissue (the tumor sample must have been collected after the most recent progression or recurrence) will be obtained from all ~~patients~~ **subjects**. If subject consents to collection of fresh baseline biopsy, it may be acquired any time during the Screening period, before administration of the 1st dose of ~~H3B-6545 and palbociclib~~**study drug** on Cycle 1 Day 1. • At baseline, Cycle 1 Day 1, **Cycle 1 Day 21, Cycle 3 Day 1,** and every 8 weeks thereafter (coinciding with CT/MRI tumor assessments schedule until **radiological** progression), and **at** end of treatment (EOT**, if different from date of progression**), whole blood samples for mutation characterization **from cell-free DNA (cfDNA)** will be collected.
	Synopsis and Section 9.8.1.1.2, Secondary Endpoints Added secondary endpoint for CBR and removed DCR: • CBR, defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response, or durable stable disease (duration is at least 23 weeks) • DCR, defined as the proportion of subjects achieving a best response of CR, PR, or stable disease
	Synopsis and Section 9.8.1.6.2, Secondary Efficacy Analyses Added CBR and removed DCR: All efficacy parameters will be summarized descriptively for the RES and FAS. ORR and ~~DCR~~ **CBR** will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson. DoR will be calculated for subjects achieving a best overall response of confirmed PR+CR. For DoR, PFS, and OS, medians will be calculated using Kaplan-Meier estimates. DoR, PFS, and OS will be reported in both summary tables and plotted with Kaplan-Meier curve.
	Synopsis and Section 9.8.1.8, Safety Analyses Clarifications for DLT assessments: The determination of the MTD **and/or RP2D** will be based on Dose Evaluable Set that consists of all DLT evaluable subjects. ~~Subjects who do not receive study drug for at least 75% of the planned dose from Cycle 1 Day 1 to Cycle 2 Day 8, for reasons not considered to be a DLT by both the investigators and the sponsor will be replaced. Subjects who are~~

	~~replaced will not be considered evaluable for DLT assessments.~~**Subjects not evaluable for DLT assessment will be replaced.**
	Section 4.1, Institutional Review Boards/Independent Ethics Committees Updated end of study time: The definition of the end of the study will be the cutoff date for the final analysis, ~~which~~ will be~~ either 12~~ **24** months after enrollment of the last subject ~~in the expansion phase or the end-of-treatment visit date for the last subject in the study, whichever occurs first~~.
	Section 6, Study Registration Added new section: **The subject must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, and the potential benefits, alternatives, side effects, risks, and discomforts. Human protection committee (Institutional Review Board [IRB]/Ethics Committee [EC]) approval of this protocol and consent form is required. Eligible subjects who wish to participate in the study will be enrolled into the study.** **In Phase 1 of the study, the Sponsor or designee will notify sites via email when a new Dose Level/Cohort is opened and enrollment slot(s) becomes available. As soon as a potential subject has been identified following the slot availability announcement, sites will notify the Sponsor or designee via email. Sponsor or designee will reply to verify an available slot and reserve the slot for the subject. Upon receipt of confirmation, sites will have 5 business days to consent the identified subject. If a subject is not consented within 5 business days, the slot will open to all sites for enrollment. A patient is enrolled once the approved enrollment packet is returned to the site in ePIP.** **The Sponsor or designee will also communicate to all sites via email when a cohort has been fully reserved and screening is closed. This communication may also include language that describes any opportunity for additional screening should a subject screen-fail and/or meet replacement criteria.** **Once a site receives confirmation of successful slot reservation, the subject may be consented, and screening procedures may begin. All screening procedures must be completed as outlined in the protocol, and the PI must assess and confirm eligibility of the subject prior to requesting enrollment. Once eligibility is confirmed by the PI and Sponsor or designee, subject registration and dose level assignment will be performed by the Sponsor or designee. The Sponsor or designee will document the subject identification number, dose level, and date of enrollment on the registration form, and will send the completed form back to the site as soon as possible, no later than 24 hours following the registration request.** **All subject data collected in the study will be stored under this number. Only the investigator will be able to link the subject's study data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification**

by the Monitor, audits, and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

Section 7.2.1, H3B-6545

Updated G4 value for serum bilirubin:

	100 – 300 mg (N=29)			450 mg (N=21)		
Adverse Event	**G2**	**G3**	**G4**	**G2**	**G3**	**G4**
Neutropenia	0	0	0	0	0	0
Thrombocytopenia	0	3	0	0	0	0
Anemia	14	7	0	14	5	0
ALT	0	3	0	10	0	0
AST	3	10	0	10	0	0
Serum bilirubin	0	3	1~~3~~	5	0	0
Serum creatinine	3	0	0	0	0	0
Nausea	7	0	0	5	0	0
Vomiting	3	0	0	0	0	0
Diarrhea	7	0	0	5	5	0
Fatigue	14	0	0	5	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; G = grade.

Section 9.1, Overall Study Design and Plan and Section 9.1.3, Follow-Up Phase

Updated end of study time:

End of study will be **based on** the cutoff date for the final analysis, which will be ~~either 12~~ **24** months after enrollment of the last subject ~~in the expansion phase or the end-of-treatment visit date for the last subject in the study, whichever occurs first~~.

Section 9.1.3, Follow-Up Phase

Updated follow-up :

The follow-up phase will extend from treatment discontinuation until the End of Study (24 months after enrollment of last subject)~~ or death~~.

Section 9.5, Dose Modifications

Updated nonhematologic toxicities:

Grade 1 (asymptomatic) Heart rate <40 bpm	No dose adjustment is required	*First occurrence*: Withhold drug until heart rate is ≥50 bpm ~~or ≥ baseline value~~; resume

			drug at the same dose level *Second occurrence*: Withhold drug until heart rate is ≥50 bpm ~~or ≥ baseline value~~; resume drug at the next lower dose
	Grade 2 (symptomatic, **intervention not indicated; change in medication initiated**)	No dose adjustment is required	Withhold drug until (a) symptoms resolve and (b) heart rate is ≥50 bpm ~~or ≥ baseline value~~; resume drug at the next lower dose
	Grade 3 (**symptomatic, intervention indicated**)	Withhold palbociclib until (a) symptoms resolve and (b) heart rate is ≥50 bpm ~~or ≥ baseline value~~; resume drug at the next lower dose	Withhold drug until (a) symptoms resolve and (b) heart rate is ≥50 bpm ~~or ≥ baseline value~~; resume drug at the next lower dose
	Grade 4 (**Life-threatening consequences; urgent intervention indicated**)	Withhold palbociclib until (a) symptoms resolve and (b) heart rate is ≥50 bpm ~~or ≥ baseline value~~; resume drug at the next lower dose	Discontinue drug
	QTcF prolongation		
	Grade 3 (average: ≥501 ms; >60 ms change from baseline)	Withhold drug until average is <480 ms and <60 ms change from baseline; resume at the next lower dose	Withhold drug until average is <480 ms and <60 ms change from baseline; resume at the next lower dose

Monitor subjects for pulmonary symptoms indicative of ILD/pneumonitis (eg, hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/ pneumonitis, interrupt palbociclib immediately and evaluate the subject. Permanently discontinue palbociclib in subjects with severe ILD or pneumonitis.

Section 9.6.1.2.1, Tumor Assessments

Clarifications on disease progression:

Subjects who discontinue study treatment without **radiological** disease progression will continue to have tumor assessments as per the Schedule of Assessments until **radiological** disease progression, death, or initiation of another anticancer therapy, whichever occurs first, unless the study is terminated.

Section 9.6.1.4.3, Laboratory Measurements

Clarifications on clinical laboratory tests:

~~Urinalysis~~ **Urine Dipstick**	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

Section 9.6.1.4.6, Electrocardiograms

Clarifications on ECG assessments:

ECG assessments will be performed throughout the study. ~~Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.~~

~~For all subjects, shift tables will present changes in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) from baseline to end of treatment. In addition, summary tables and listings for the various intervals (eg, QT and pulse rate) and changes from baseline will be presented.~~

~~In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia will be categorized as follows:~~

- ~~Absolute QTcF interval prolongation:~~
  - ~~QTcF interval >500 ms~~
- ~~Change from baseline in QTcF interval:~~
  - ~~QTcF interval increases from baseline >60 ms~~

~~All ECG abnormalities will be listed on a per-subject basis.~~

Triplicate 12-lead ECG will be performed after the patient has been resting for 10 minutes prior to each timepoint indicated, and at Unscheduled visits as clinically required. The ECGs should be taken while the patient in a semi-recumbent position. At Screening, triplicate ECGs should be taken approximately 5 minutes apart. On Cycle 1 Day 1, triplicated ECGs should be performed predose. The combined QTcF values will be averaged to provide a single baseline value for each patient. This averaged value will be documented in the ECG section of the CRF. ECG measurements on Cycle 1 Day 8, Cycle 1 Day 21, and Cycle 1 Day 28 should match the PK collection. Data from local safety ECGs should be entered into the clinical database.

In addition, in the event of any alteration or if clinically indicated, additional ECGs and/or cardiac enzyme evaluations should be performed. If sinus bradycardia is observed at EOT visit, follow up ECGs should be performed weekly until heart rate has returned to 60 or more beats per minute or pre-study baseline.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 8.6.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

	For ECG abnormalities meeting the criteria of an SAE, the site must fax or email the SAE report including the ECG report to the Sponsor using the SAE form.
	Section 9.6.1.4.7, Other Safety Assessments Clarifications on multiple-gated acquisition (MUGA) scan language: A MUGA scan ~~(using technetium-99m-pertechnetate)~~ or an ECHO to assess LVEF will be performed at screening, at Cycle 3 Day 1, and if clinically indicated thereafter. MUGA scans should be performed locally in accordance with the institution's standard practice; ECHO should be performed following the protocol provided by the cardiovascular core laboratory. MUGA and ECHO electronic files will be sent to the central laboratory for analysis and archiving. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at Baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.
	Section 9.6.2.1, Schedule of Procedures/Assessments Added range for Safety Follow-up: **28 days (±7 days)** Added **Survival Follow-up** with footnote u PK samples: added "X" to EOT Added **PG whole blood**, with an "X" for Screening, D-21 to D1 cfDNA: added "X" for Cycle 1 D21 CT)/MRI scans: clarifications for disease progression: Every 8 weeks ~~or~~ **until radiological disease progression and** as clinically indicated Brain scan: added "X" for EOT
	Section 9.6.2.1, Schedule of Procedures/Assessments a All subjects will be followed for survival approximately every 3 months for up to 24 months after enrollment of the last subject. Additional survival data may be requested prior to ~~the~~**interim or** main ~~analysis~~**analyses**. Subjects will be followed for adverse events for 28 days after the last treatment administration. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered on treatment until they discontinue the 2nd drug. b With the exception of triplicate 12-lead ECG and cfDNA, other assessments performed during the 7 days prior to Cycle 1 Day 1 should need not be repeated, unless otherwise indicated. **On Cycle 1 Day 1, scheduled ECG, vital signs, and laboratory test should be performed predose.** c Cycle 2 Day 1 laboratory values for CBC/CMP, INR/PT/aPTT, and urine testing dipstick, can be drawn on Cycle 1 Day 28, in conjunction with the PK blood draw. d Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature). Height will be recorded at the baseline visit only.

	e A standard 12-lead ECG will be performed after the patient has been resting for 10 minutes prior to each timepoint indicated. The ECGs should be taken while the patient in a semi-recumbent position. At Screening, triplicate ECGs should be taken approximately 5 minutes apart. **On Cycle 1 Day 1, triplicated ECGs should be performed predose. The combined QTcF values will be averaged to provide a single baseline value for each patient. This averaged value will be documented in the ECG section of the CRF. ECG measurements on Cycle 1 Day 8, Cycle 1 Day 21, and Cycle 1 Day 28 should match the PK collection.** e**f** ~~The combined QTcF values will be averaged to provide a single baseline value for each patient. This averaged value will be documented in the ECG section of the CRF.~~ At screening, at Cycle 3 Day 1, and if clinically indicated thereafter. ~~f~~**g** Pregnancy test during the screening period should be serum (no need to repeat on Cycle 1 Day 1 if within 72 hours). During the study, urine testing should be performed at Day 1 of each cycle or serum testing should be performed to confirm a positive urine testing. ~~g~~**h** CBC count consisting of hematocrit, hemoglobin, total WBC with 5-part differential, and platelet count plus RBC count. ~~h~~**i** CMP panel includes the following: glucose, calcium, albumin, total protein, electrolytes (sodium, potassium, carbon dioxide, and chloride), renal function tests (blood urea/blood urea nitrogen, and creatinine), and liver function tests (ALP, ALT, AST, and bilirubin). ~~i~~**j** Other includes the following: albumin, CRP, fasting lipase, fasting amylase, lactate dehydrogenase, magnesium, phosphorus, gamma-glutamyl transpeptidase, and thyroid function tests (TSH and free T4). ~~j~~**k** INR, PT, aPTT will be assessed by standard methods at a local laboratory. l **See Appendix 3 for HBV/HCV testing criteria.** ~~k~~**m** If abnormalities are present, microscopic testing should be done. ~~l~~**n** H3B-6545: daily starting Cycle 1 Day 9; palbociclib: daily from Day 1 to Day 21 every 28-day cycle. ~~m~~**o** Plasma samples for pharmacokinetics: a. During the escalation part of the study: On Cycle 1 Day 8, PK blood samples to determine plasma concentrations of palbociclib will be collected at predose~~ and 1, 2, 4, 6, 8, and 24 hours postdose.~~ **(within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.** On Cycle 1 Day 21, PK blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. On Cycle 1 Day 28, PK blood samples to determine plasma concentrations of H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. b. During the expansion phase: On Cycle 1 Day 21, PK blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be

	collected predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of **the** next day's dose of study drugs) postdose. These windows apply to PK sampling on other days. c. During both phases of the trial: additional PK blood samples will be collected in conjunction with tumor assessments until ~~disease progression~~**EOT**. d. **Samples should be collected via peripheral vein when possible.** ~~n~~**p** New biopsy (preferred) or archival tumor block or slides (15 slides minimum from a surgical specimen, 20 slides minimum from a biopsy) must be provided. If archival tissue is provided, the tumor sample must have been collected after the most recent progression or recurrence. ~~o~~**q** Whole blood for cfDNA (8 mL) will be collected during the screening period, Cycle 1 Day 1, **Cycle 1 Day 21, Cycle 3 Day 1,** every 8 weeks thereafter (in conjunction with tumor assessments)**,** and EOT. Two tubes (2x8 mL) will be collected at Screening and EOT. ~~p~~**r** A bone scan using whole-body bone MRI, ^{99}m-technetium-based bone scans, or ^{18}F-sodium fluoride positron emission tomography will be performed during Screening to establish a baseline (a historical bone scan performed within 6 weeks before Cycle 1 Day 1 is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging. ~~q~~**s** Tumor assessments (CT of the chest with and without IV contrast and CT [oral and IV contrast] or MRI [IV contrast] of the abdomen, pelvis, and other known or suspected sites of disease) will be performed during Screening (Day -21 to Cycle 1 Day 1) and every 8 weeks (±7 days) after Cycle 1 Day 1 (ie, 8, 16, 24 weeks) or as indicated if disease progression is suspected clinically. ~~r~~**t** A brain scan (CT with contrast or MRI [pre- and postgadolinium]) will be performed at Screening and as clinically indicated to assess potential for central nervous system disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment timepoints, including EOT. For all subjects, a follow-up brain scan must be performed to confirm CR within 1 week following response confirmation or if clinically indicated. **u Following progression, all subjects will be followed for survival every 12 weeks or more often if requested prior to interim or final analysis. The follow-up can be done by telephone call at the investigator's discretion.**
	Section 9.6.4.6, Regulatory Reporting of Adverse Events Clarifications on palbociclib Reference Safety Information: For this study, the Reference Safety Information for palbociclib, which the sponsor will use to assess expectedness, is the approved palbociclib (Ibrance) EMA SmPC ~~and palbociclib (Ibrance USPI, 2019)~~.

<table>
<tr><td></td><td>Section 9.8.1.8.1, Extent of Exposure
Clarifications on extent of exposure language:
Descriptive statistics for subjects treated, including the duration of treatment, ~~the number of cycles received,~~ and the number of subjects requiring dose changes, will be presented. A by-subject listing of the date of study drug administration and the dose administered will be presented. Details will be provided in the SAP.</td></tr>
<tr><td></td><td>Section 9.8.1.8.3, Laboratory Values
Clarifications on laboratory values language:
Furthermore, the frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be tabulated~~ by cycle and overall~~ for selected laboratory parameters to include at least, hemoglobin, WBC, ANC, lymphocytes, platelet count, ALP, AST, ALT, bilirubin, creatinine, and electrolytes. Shift tables will also be produced for these parameters based on the baseline CTCAE grade and the maximum CTCAE grade ~~by cycle and overall~~post baseline. Details will be provided in the SAP.</td></tr>
<tr><td></td><td>Section 9.8.1.8.5, Electrocardiograms
Clarifications on electrocardiograms language:
ECG assessments will be performed ~~at each visit~~ throughout the study according to the schedule of assessments. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.
~~Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment. In addition, summary~~Summary tables and listings for the various intervals (eg, QT and pulse rate) and changes from baseline will be presented. Additional analysis will be detailed in the SAP.</td></tr>
<tr><td></td><td>Appendix 3, HBV/HCV Testing Criteria
Added new appendix:
Eligibility Based on Serologic Markers for Hepatitis B and Hepatitis C
<table>
<tr><th>Test</th><th>Result</th><th></th><th></th><th></th><th></th></tr>
<tr><td>HBsAg</td><td>+</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>HBcAb</td><td>Any</td><td>+</td><td>-</td><td>+</td><td>-</td></tr>
<tr><td>HBsAb</td><td>Any</td><td>-</td><td>+</td><td>+</td><td>-</td></tr>
<tr><td>HCV Ab</td><td>Any</td><td>Any</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Eligibility</td><td>Not Eligible</td><td>Not Eligible</td><td>Eligible</td><td>Eligible</td><td>Eligible</td></tr>
</table>
If indeterminate results are obtained, viral DNA (hepatitis B) or RNA (hepatitis C) should be measured to confirm negative viral status.</td></tr>
</table>

	HCV Ab positive: Indicates active infection and risk for reactivation. These patients are not eligible for this trial. **HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These patients are not eligible for this trial.** **HBcAb positive and HBsAb negative: indicate active infection and risk for reactivation. These patients are not eligible for this trial.** **HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if it is the only positive finding. These patients are eligible for this trial.** **HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These patients are eligible for this trial.** **All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Patients are eligible for this trial**

Date	**Highlights of Major Changes**	
15 June 2021	**Amendment 03**	
Deletions are shown as ~~strikethrough~~; new content is shown in **bold.**		
	Section Affected, Description of Change	**Rationale**
	Synopsis; Section 9.1, Overall Study Design and Plan Updated description of a cohort: Each cohort will consist of 6 **DLT-evaluable** subjects to ensure sufficient safety and PK data are obtained prior to dose escalation. Synopsis table; Section 9.1, Overall Study Design and Plan Table 3 Updated table column header: Number of **DLT-Evaluable** Subjects Synopsis Updated description of SRC review: After **6 DLT-evaluable** ~~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.	To clarify the number of evaluable subjects required to complete evaluation of a treatment cohort.
	Synopsis; Section 9.6.1.2.1, Tumor assessments; Section 9.6.2.1, Schedule of Procedures/Assessments Table 8 footnote s	To clarify the description of tumor assessment requirements.

	Updated description of tumor assessments: Tumor assessments (~~computed tomography [~~CT~~]~~ ~~of the~~ chest with ~~and without intravenous [~~IV~~]~~ contrast and CT ~~[~~(oral and IV contrast)~~]~~ or magnetic resonance imaging [MRI] (IV contrast) of the abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Screening/Baseline period (Day -21 to Cycle 1 Day 1). **If imaging with contrast, as requested in above, is contraindicated, imaging without contrast should be performed and reason for contraindication should be captured in the source documents**.	
	Synopsis; Section 9.6.1.3.1, Pharmacokinetic Assessments; Section 9.6.2.1, Schedule of Procedures/Assessments Table 8 footnotes (o) Amended Pharmacokinetic Assessments: In dose escalation: On Cycle 1 Day 8, PK **(palbociclib)** blood samples to determine plasma concentrations of palbociclib will be collected at predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days. On Cycle 1 Day 21, PK **(palbociclib and H3B 6545)** blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. On Cycle 1 Day 28, PK **(H3B 6545)** blood samples to determine plasma concentrations of H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. During the treatment phase, PK **(palbociclib and H3B 6545)** blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until end of treatment (EOT). In dose expansion: On Cycle 1 Day 21, PK **(palbociclib and H3B 6545)** blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose (within 1 hour before	To clarify samples to be taken for PK assessment.

	administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days. During the treatment phase, PK **(palbociclib and H3B 6545)** blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until progression.	
	Synopsis Amended Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments: • At baseline (during screening), pretreatment fresh biopsies or archival tumor tissue (the tumor sample must have been collected after the most recent progression or recurrence) will be obtained from all subjects. If a subject consents to collection of fresh baseline biopsy, it may be acquired any time during the Screening period, before administration of the 1st dose of study drug on Cycle 1 Day 1. **If collection of a biopsy during the screening period poses disproportionate risk to subject's safety, the reason for the contraindication must be documented in source at site. Once documentation detailing risk is captured in the site records, subject may continue screening and if all I/E criteria are met, subject may be enrolled and treated.** Section 9.6.1.1, Screening Assessments • Collection of pretreatment fresh biopsies or archival tumor tissue (the tumor sample must have been collected after the most recent progression or recurrence). **If collection of a biopsy during the screening period poses disproportionate risk to subject's safety, the reason for the contraindication must be documented in source at site. Once documentation detailing risk is captured in the site records, subject may continue screening and if all I/E criteria are met, subject may be enrolled and treated.**	To describe the procedure to be followed if collection of a biopsy poses disproportionate risk to subject.

	Section 9.1, Overall Study Design and Plan Amended description of allocation of subjects to treatment cohorts: The dose escalation part of the study will determine the MTD and/or the RP2D of H3B-6545 in combination with palbociclib. Each cohort will consist of 6 subjects to ensure sufficient safety and PK data are obtained prior to dose escalation. A cycle of treatment will be 28 days. **Due to the potential for screen failures and/or a subject discontinuing treatment before completion of the cohort DLT assessment window (non-evaluable for DLT assessment), up to 8 slots will be opened for screening in order to obtain 6 DLT-evaluable subjects (see Section 9.1). In addition, subjects considered screen failures or unevaluable for DLT will be replaced.** **Once 6 subjects have been dosed at the current cohort dose level, any additional subjects in screening will be allocated to one of the following cohorts for enrollment:** • **The current cohort so that the total number of DLT-evaluable subjects is maintained at 6, if any of the 6 already dosed subjects becomes non-evaluable for DLT;** • **A lower dose cohort which has already been deemed safe per dose escalation meeting, if none of the 6 already dosed subjects becomes non-evaluable for DLT in the cohort currently under evaluation; the additional subject(s) will not contribute to DLT evaluation of the lower dose cohort, but will contribute to the overall safety evaluation.** • **The next cohort to be opened to enrollment including the expansion cohort if the RP2D has been reached and the expansion phase is open to enrollment** **Sponsor approval of any enrollment scenario not described above must take place prior to screened subject enrollment.** In the 1st cycle, palbociclib will be administered PO QD on Days 1 to 21 and H3B 6545 will be 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.	To describe in more detail the process for allocation of subjects to treatment cohorts on completion of screening.

<table>
<tr><td></td><td>Section 9.1, Overall Study Design and Plan Table 4
Hepatic: ALT or AST criterion for defining Dose-Limiting Toxicity changed from ≥ 8 × ULN to >8 × ULN</td><td>To correct an inconsistency.</td></tr>
<tr><td></td><td>Section 9.1.3 Follow-Up Phase
Added language for Extension Phase</td><td>To clarify safety assessments for subjects who will remain on study treatment after the data cutoff date for the planned final PFS analysis (24 months after the last patient receives their first dose). All subjects who are still on study treatment at that time will enter the Extension Phase</td></tr>
<tr><td></td><td>Section 9.5, Dose Modifications
Added further detail of dose reductions:
Recommendations for dose reduction, interruption or discontinuation of either drug in the management of adverse reactions are summarized in Table 5 (hematologic toxicities) and Table 6 (non-hematologic toxicities). Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
Two dose reductions of H3B-6545 (450 mg to 300 mg, then to 150 mg QD) for toxicity will be allowed as per the guidance summarized in Table 5 and Table 6. If persistent toxicity occurs despite two dose reductions, the subject will discontinue study treatment
Two dose reductions for palbociclib (125 mg to 100 mg, then to 75 mg QD) for toxicity will be allowed (Table 5 and Table 6). If persistent toxicity occurs despite two dose reductions, the subject will discontinue study treatment.</td><td>To provide further detail of H3B-6545 dose reductions and to simplify the dose reduction guidance to multiples of 150 mg.</td></tr>
<tr><td></td><td>Section 9.5, Dose Modifications
Table 5 Dose Modifications and Management Recommendation – Hematologic Toxicities
<table>
<tr><th>CTCAE Grade</th><th>Palbociclib</th><th>H3B-6545</th></tr>
<tr><td>Anemia</td><td></td><td></td></tr>
<tr><td>Grade 4</td><td>Withhold dose until recovery to Grade ≤2;</td><td>Withhold dose until</td></tr>
</table></td><td>Hematologic toxicities are not predicted to be associated with H3B-6545 treatment.
Dose modification of H3B-6545 is not predicted to be of benefit in the management of hematologic toxicities.</td></tr>
</table>

	resume drug at next lower dose	**recovery to Grade ≤2; resume drug at next lower dose** ~~Withhold dose until recovery to Grade ≤2; resume at the same dose~~
Grade 3	• Day 1 of cycle: Withhold drug, repeat complete blood cell count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. • Day 15 of first 2 cycles: Continue palbociclib at current dose to complete cycle and repeat complete blood cell count on Day 22.	**Withhold dose until recovery to Grade ≤2; resume drug at next lower dose** ~~Withhold dose until recovery to Grade ≤2; resume at the same dose~~
Grade 1 or 2	No dose adjustment is required	No dose adjustment is required
All Other Hematological Toxicity		
Grade 4	**Withhold dose until recovery to Grade ≤2; resume drug at next lower dose**	**No dose adjustment is required.**
Grade 3	• **Day 1 of cycle: Withhold drug, repeat complete blood cell count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose.** • **Day 15 of first 2 cycles: Continue palbociclib at current dose to complete cycle and repeat complete blood cell count on Day 22.**	**No dose adjustment is required.**
Grade 1 or 2	**No dose adjustment is required**	**No dose adjustment is required**

Grade 3 neutropenia with fever ≥38.5 °C and/or infection	Withhold palbociclib until recovery to Grade ≤2; resume at the next lower dose	Withhold dose until **fever subsides** ~~recovery to Grade ≤2~~; resume at the same dose	
	Section 9.5, Dose Modifications Dose modifications for use with strong CYP3A inhibitors • Reduce the H3B-6545 dose to **150**~~200~~ mg QD		To simplify the dose reduction guidance for use with strong CYP3A inhibitors to multiples of 150 mg
	Section 9.6.1.4.3, laboratory measurements Table 7 Table 8 footnote i In the Comprehensive Metabolic Panel, ~~Glucose~~ updated to **Fasting glucose**.		To reduce the potential variability of glucose test results.
	Section 9.6.1.4.6, Electrocardiograms ECG assessments will be performed ~~throughout the study~~ **in triplicate for all study visits where ECGs are required and ECGs should be collected predose on days where PK samples are not collected (Table 8 Schedule of Procedures/Assessments in Study H3B-6545-G000-102)**.		To clarify the requirements for ECG assessments.
	Section 9.6.1.4.7, Other Safety Assessments A MUGA scan or an ECHO to assess LVEF will be performed at screening, at Cycle 3 Day 1, and if clinically indicated thereafter. MUGA scans should be performed locally in accordance with the institution's standard practice; ECHO should be performed following the protocol provided by the cardiovascular core laboratory. ~~MUGA and ECHO electronic files will be sent to the central laboratory for analysis and archiving.~~ MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at Baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.		Central laboratory analysis and archiving of MUGA and ECHO electronic files are not required.
	Section 9.6.2.1, Schedule of Procedures/Assessments Table 8 footnotes e A standard 12-lead ECG will be performed after the patient has been resting for 10 minutes prior to each timepoint indicated. The ECGs should be taken while the patient in a semi-recumbent		To clarify procedures. (Other footnote changes are described above)

	position. At Screening, triplicate ECGs should be taken approximately 5 minutes apart. On Cycle 1 Day 1, triplicated ECGs should be performed predose. The combined QTcF values will be averaged to provide a single baseline value for each patient. This averaged value will be documented in the ECG section of the CRF. ECG measurements on Cycle 1 Day 8, Cycle 1 Day 21, and Cycle 1 Day 28 should match the PK collection. **Triplicate ECGs are to be performed at all visits indicated and should be collected predose on C3D1 and D1 of all subsequent cycles. C1D28 24-hour ECG can also meet the requirement for C2D1 ECG.** p New biopsy (preferred) or archival tumor block or slides (15 slides minimum from a surgical specimen, 20 slides minimum from a biopsy) must be provided. If archival **tumor** tissue is provided, the tumor sample must have been collected after the most recent progression or recurrence. **Not required for subjects with bone only disease** v **Any protocol assessment, including labs, performed within 3 days prior to D1 of the next cycle do not need to be repeated on D1 of the new cycle.**	
	New Section added **9.6.4.1 REPORTING OF ABNORMAL HEPATIC TESTS OF CLINICAL INTEREST** **The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.6.4.2). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."** **1. Elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN or if elevated greater than the ULN at baseline, then 3× the baseline for the subject** **AND** **2. Elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN or if elevated greater than the ULN at baseline, then 1.5× the baseline for the subject**	To provide detail of the procedure for identifying and reporting abnormal hepatic tests of clinical interest.

	AND AT THE SAME TIME **3. Alkaline phosphatase laboratory value that is less than 2× the ULN** ***Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.** **Table 9 Extension Phase Assessment table added**	
	Section 9.6.5 Completion/Discontinuation of Subjects Qualification added to list of reasons for treatment discontinuation: ****Subjects may continue to receive treatment after progression only if, after discussion with the medical monitor, it is determined that the subject continues to derive clinical benefit.***	To clarify that subjects with disease progression may continue to receive treatment if the subject continues to derive clinical benefit.
	Section 12, Appendices Appendix 1, Concomitant Medications: Use of antacids is allowed~~ but should be administered ≥2 hours before or ≥4 hours after H3B-6545~~. The use of palonosetron for the management of nausea and vomiting is also allowed	For consistency with changes introduced in Amendment 2.0.

Date	**Highlights of Major Changes**	
29 August 2022	**Amendment 04**	
	Sections Affected, Description of Changes	**Rationale**
	The primary analysis data cutoff will occur 6 months after the last subject receives their first dose. Changed the "main analysis" wording to "primary analysis". - Protocol Synopsis, Overall Study Design - Protocol Synopsis, Efficacy Assessments - Section 9.1 Overall Study Design and Plan - Section 9.1.3 Follow-up Phase	To clarify the primary analysis data cutoff will occur 6 months after the last subject receives their first dose, and to no longer perform the previously planned final overall

	- Section 9.6.2.1 Schedule of Procedures/Assessments, Table 9	survival analysis at 24 months. Further development of H3B-6545 is not planned at this time.
	Survival follow-up will end at the primary analysis data cutoff and clarified the survival follow-up will not be done in the Extension Phase. The first anti-cancer therapy following treatment discontinuation will be recorded up until the data cutoff for the primary analysis - Protocol Synopsis, Overall Study Design - Section 9.1.3 Follow-up Phase - Section 9.3.3 Removal of Subjects From Therapy or Assessment - Section 9.6.2.1 Schedule of Procedure/Assessments, Table 8 footnotes a and u	
	Pharmacokinetic and biomarker sample collection will no longer be performed and the data cutoff date for the primary analysis. - Protocol Synopsis, Pharmacokinetic Assessments, Biomarker Assessments - Section 9.6.1.3.1 Pharmacokinetic Assessments - Section 9.6.1.3.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments - Section 9.6.2.1 Schedule of Procedures/Assessments, Table 8, footnotes o (c.) and q	To align with the primary analysis cutoff date.
	The end of study definition is clarified. - Section 4.1 Institutional Review Boards/Independent Ethics Committees; removed end of study definition here because this is not required to be defined in this section - Section 9.1 Overall Study Design and Plan	For clarification and consistency.
	Specified the visit (Cycle X Day 1) in the Extension Phase schedule of assessments. - Section 9.6.2.1 Schedule of Procedures/Assessments, Table 9, footnote a.	For clarification.
	H3 Biomedicine Inc. is removed from the protocol. Eisai, Inc. remains as the Sponsor. - Title page - Section 5 Investigators and Study Personnel	Revised to clarify the current Sponsor since this Eisai subsidiary is being closed.
	Minor editorial changes (grammar, formatting), throughout	To enhance clarity and consistency

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. H3B-6545

Name of Active Ingredient: H3B-6545 and palbociclib

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

Investigator(s)

Global Principal Investigator: Stephen R. D. Johnston, MA, FRCP, PhD

The Royal Marsden NHS Foundation Trust, 203 Fulham Road, Chelsea, London, SW3 6JJ, UK

Sites

Global, approximately 7 centers

Study Period and Phase of Development

Approximately 24 months,
Phase 1b dose escalation with dose expansion

Objectives

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 estrogen receptor–positive (ER+) human epidermal growth factor receptor-2–negative (HER2–) breast cancer.

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; complete response [CR], partial response [PR], or stable disease ≥23 weeks), progression-free survival (PFS), and overall survival (OS)

Exploratory Objective

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

Study Design

Overall Design:

This is a multicenter, open-label, dose escalation and dose expansion study of H3B-6545 in combination with palbociclib for women with advanced or metastatic ER+ HER2– breast cancer.

End of study: The cutoff date for the primary analysis will be approximately 6 months after the last subject receives their first dose of study treatment. The end of study will be the last assessment for the last subject (eg, the last assessment in the Extension Phase)

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.

Subjects who are tolerating therapy and are without progressive disease may receive treatment until progression.

Dose escalation will determine the MTD and/or the RP2D of H3B-6545 in combination with palbociclib. Due to the potential for screen failures and/or a subject discontinuing treatment before completion of the cohort DLT assessment window (non-evaluable for DLT assessment), up to 8 slots will be opened for screening in order to obtain 6 DLT-evaluable subjects (See Section 9.1). In addition, subjects considered screen failures or unevaluable for DLT will be replaced. Each cohort will consist of 6 DLT-evaluable subjects to ensure sufficient safety and PK data are obtained prior to dose escalation. A cycle of treatment will be 28 days.

In the 1st cycle, palbociclib will be administered orally (PO) once daily (QD) on Days 1 to 21 and H3B-6545 will be 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.

A maximum of 4 dose levels are planned, with palbociclib escalated no higher than 125 mg QD and H3B-6545 escalated no higher than 450 mg QD (RP2D).

Dose Escalation Table

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

DLT= dose-limiting toxicity; 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 1st day of adding H3B-6545 to palbociclib (Cycle 1 Day 9 to Cycle 2 Day 8). Subjects who do not receive at least 75% of the scheduled therapy from Cycle 1 Day 9 to Cycle 2 Day 8, for

reasons other than toxicity, will not be considered evaluable for DLT assessment and will be replaced. Disease progression and adverse events (AEs) deemed related to disease progression will not be considered DLTs.

After 6 DLT-evaluable 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.

- **Cohort 1:** If none or only 1 subject experienced a DLT, initiate enrollment in Cohort 2. If 2 or more subjects experienced a DLT, initiate enrollment in Cohort -1.
- **Cohort -1:** If none or only 1 subject experienced a DLT, the doses used in Cohort –1 will be considered the RP2D. If 2 or more subjects experienced a DLT, the combination of H3B-6545 and palbociclib at clinically meaningful doses will be considered unfeasible.
- **Cohort 2:** If none or only 1 subject experienced a DLT, initiate enrollment in Cohort 3. If 2 or more subjects experienced a DLT, the doses used in Cohort 1 will be considered the MTD and the RP2D.
- **Cohort 3:** If none or only 1 subject experienced a DLT, doses used in this Cohort will be considered the RP2D. If 2 or more subjects experienced a DLT, consideration will be given to opening cohort 3b depending upon observed toxicity profile.
- **Cohort 3b:** If none or only 1 subject experienced a DLT, doses used in this Cohort and in Cohort 2 could be considered the RP2D. In this case, the SRC will select between Cohort 2 and Cohort 3b for the expansion phase. If 2 or more subjects experienced a DLT, doses used in Cohort 2 will be considered the RP2D.

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 data, for all dose levels tested.

DLTs: Unless considered not related to study drugs, any of the following criteria will qualify as a DLT:

Toxicity	Criteria[a]
Hematology	- Febrile neutropenia (ANC $<1\times10^9$/L and fever ≥38.5 ° C) - Grade 4 neutropenia that does not resolve to Grade ≤2 (ANC $\geq1\times10^9$/L) within 7 days; use of GM-CSF is allowed - Grade 4 thrombocytopenia ($<25.0\times10^9$/L) - Grade 3 thrombocytopenia ($25.0 – 50.0\times10^9$/L) lasting more than 7 days or associated with clinically significant bleeding
Vomiting	- CTCAE Grade 4 vomiting - Grade 3 vomiting lasting >72 hours despite optimal antiemetic treatment
Diarrhea	- CTCAE Grade 4 diarrhea - Grade 3 diarrhea lasting >72 hours despite optimal antidiarrheal treatment

Electrolytes abnormality	- Grade 4 - Grade 3 lasting for more than 24 hours Note: Grade 3 that lasts <24 hours and resolves spontaneously or responds to conventional medical interventions is not considered a DLT.
Renal	- Grade 3 or 4 serum creatinine
Hepatic	- Grade 3 or 4 bilirubin increase - ALT or AST >8 × ULN - In absence of liver metastases at baseline and in absence of clinical or radiological evidence of biliary obstruction: ALT or AST >3 × ULN, in conjunction with total bilirubin >2 ×ULN
Biochemistry	- Grade 4 - Grade 3 lasting more than 7 days, unless considered not clinically significant as per the discretion of the investigator
Any other non-hematologic AE	Grade 4 Grade 3 (except diarrhea, rash, nausea, or vomiting lasting ≤72 hours) Any drug-related intolerable Grade 2 toxicity (other than hematological AEs) leading to administration of <75% of the dose during the DLT observation period

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; GM-CSF = granulocyte–macrophage colony-stimulating factor; ULN = upper limit of normal.

a. Laboratory values that meet criteria listed in this table should be repeated and confirmed within 24 hours of the initial results being reported.

Intrasubject dose escalation: Once a subject has completed Cycle 3 at her assigned dose level of drug, intrasubject dose escalation will be allowed. No more than 2 dose escalations are allowed for any subject. Only subjects who have not progressed on treatment and did not have a dose reduction of either palbociclib or H3B-6545 because of AEs can escalate to the highest dose level that has completed DLT assessment and has been shown to be safe (no more than 1 DLT in 6 subjects). Subjects on the intra-subject dose escalation will not be included in the DLT analysis at the higher dose level.

Dose expansion: 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.

AEs will be managed by treatment interruption, dose reduction, and/or treatment discontinuation in accordance with the dose modification instructions outlined in the protocol. Treatment will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent.

Number of Subjects

Dose escalation – Total sample size will be determined based upon the number of DLTs observed and the number of dose levels (cohorts) studied. Dose escalation may accrue approximately 12 to 24 subjects.

Dose expansion will enroll 12 additional subjects at the RP2D. Therefore, the study is expected to enroll approximately 24 to 36 subjects.

Inclusion Criteria

1. Subject has signed informed consent form before any study-related activities and according to local guidelines.
2. Female, aged ≥18 years, at the time of informed consent
3. Subject has histopathologically or cytologically confirmed ER+ HER2– locally advanced, recurrent, or metastatic breast cancer, as per local laboratory
4. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Subjects enrolling to the study who do not have measurable disease at baseline per RECIST 1.1 guidelines may be enrolled if they have at least 1 mainly lytic bone lesion, provided that the lesion has not been irradiated, or exhibits demonstrable progression since irradiation.
5. Prior therapy in the advanced or metastatic setting:
   a. Dose escalation: 2 or more prior hormonal therapies. Subjects may have received up to 1 prior chemotherapy regimen and up to 1 prior CDK4/6 inhibitor.
   b. Dose expansion: Up to 2 prior endocrine therapies and up to 1 prior chemotherapy regimen but may not have received a prior CDK4/6 inhibitor.

   Note: If the patient was enrolled within 12 months of the end of adjuvant therapy, the adjuvant therapy will also be counted.

   Note: Subjects must have documented progression while on or after the most recent therapy.
6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Life expectancy >12 weeks, as per investigator's best assessment, during the Screening phase.
8. Subject has adequate bone marrow and organ function, as defined by the following laboratory values:
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   b. Platelets $\geq 100 \times 10^9$/L
   c. Hemoglobin ≥9.0 g/dL (may have been transfused)
   d. Potassium, sodium, calcium (corrected for serum albumin), and magnesium Common Terminology Criteria for Adverse Events (CTCAE) ≤Grade 1
   e. International normalized ratio ≤1.5
   f. Serum creatinine ≤1.5× upper limit of normal (ULN)
   g. Serum albumin ≥3.0 g/dL (≥30 g/L)

h. In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0×ULN. If the patient has liver metastases, ALT and AST ≤5×ULN
i. Total serum bilirubin <1.5×ULN except for patients with Gilbert's syndrome who may be included if the total serum bilirubin is ≤3.0×ULN or direct bilirubin ≤ 1.5×ULN

9. Willingness and ability to comply with study and follow-up procedures.
10. No concurrent antineoplastic therapy. Use of bone-modifying agents, including bisphosphonate and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors is permitted.

Exclusion Criteria

1. Known central nervous system (CNS) metastases, including meningeal carcinomatosis. Brain or subdural metastases are not allowable, unless the patient has completed local therapy and has discontinued the use of corticosteroids for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
2. Subject has a concurrent malignancy or malignancy within 3 years of enrollment, with the exception for basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has completed curative therapy), or known human immunodeficiency virus infection.
3. Uncontrolled significant active infections. Note: subjects with hepatitis B virus and/or hepatitis C virus infection must have undetectable viral load during screening.
4. Major surgery or other locoregional treatment within 4 weeks before the 1st dose of study drug.
5. Inability to take oral medication, or presence of malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of H3B-6545. Palbociclib contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
6. Currently participating in another clinical study or has received other investigational drugs within 28 days.
7. Active cardiac disease or a history of cardiac dysfunction, including any of the following:
   a. History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry.
   b. History of documented congestive heart failure (New York Heart Association functional classification III or IV).
   c. Documented cardiomyopathy.
   d. Subject has a left ventricular ejection fraction <50% as determined by multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO).
   e. History of any cardiac arrhythmias in the previous 12 months.
   f. A prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 ms as demonstrated by a repeated ECG; a history of risk factors for Torsade de

pointes (eg, heart failure, hypokalemia, family history of long QT syndrome) or the use of concomitant medications that prolonged the QTcF interval.

g. Subject has resting pulse rate <60 bpm

8. Females of childbearing potential who:

- Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
  a. Double-barrier contraception (considered acceptable method but not highly effective)
  b. Total abstinence (if it is their preferred and usual lifestyle)
  c. An intrauterine device
  d. Have a vasectomized partner with confirmed azoospermia.
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days (or 5 times the half-life of the study drug, whichever is longer) after study drug discontinuation.

  Note: All females will be considered to be of childbearing potential unless they are postmenopausal (has amenorrhea for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

9. Known intolerance to either study drug or any of the excipients.
10. Subject received in the 7 days prior to the administration of study drug or is currently receiving any of the following medications:
    a. Known strong inducers or inhibitors of cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp).
    b. Medications that have a narrow therapeutic window and are breast cancer resistance protein (BCRP) substrate.
    c. Medications that have a known risk to prolong the QT interval or induce Torsades de Pointes.
    d. Medications that have a narrow therapeutic window and are predominantly metabolized through CYP2C8, CYP2C9, CYP2C19, or CYP3A4.
    e. Herbal preparations/medications; these herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng.
11. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] (or hCG) test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of the study drug.
12. Active interstitial lung disease (ILD) or diagnosis of ILD within the last 12 months.
13. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.

14. Exposure within the last 14 days to an individual with confirmed or probable COVID-19 or symptoms within the last 14 days or any other reason to consider the subject at potential risk for an acute COVID-19 infection.

    Note: Please consider testing for active COVID-19 infection prior to starting trial therapy according to the institution guidelines.

15. Evidence of ongoing alcohol or drug abuse.

Study Treatments

Test drug: H3B-6545 will be supplied as opaque, hypromellose shell capsules, size 4 containing 50 mg or size 1 containing 150 mg of H3B-6545 drug substance. The composition ratio of the capsule content is the same for both strengths.

H3B-6545 is administered orally. All subjects will take H3B-6545 at their assigned dose (PO, QD), in an open-label fashion, for 28-day cycles. On days that H3B-6545 will be taken with palbociclib, subjects should take H3B-6545 at the same time as palbociclib.

Palbociclib will be supplied as 125, 100, and 75 mg capsules or tablets. Palbociclib is taken PO QD for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

H3B-6545 and palbociclib should be taken with food. Subjects should be encouraged to take their dose at approximately the same time each day and within 30 minutes of completing a meal. H3B-6545 capsules and palbociclib capsules or tablets should be swallowed whole. Capsules or tablets should not be ingested if they are broken, cracked, or otherwise not intact. Dosing should not be repeated if a subject vomits. A dose missed by more than 12 hours should be skipped. The next prescribed dose should be taken at the usual time.

Duration of Treatment

Study duration for each subject is estimated to be:

- **Screening/Baseline Phase**: Up to 21 days.
- **Treatment Phase**: Subjects will continue to receive study treatment until radiological disease progression, development of unacceptable toxicity, or withdrawal of consent. Treatment beyond radiological progression may be allowed if the subject continues to have clinical benefit as per the principal Investigator after discussion and written approval from the Sponsor.
- **Follow-Up Phase**: All subjects will be followed for survival approximately every 3 months for up to 6 months after the last subject receives their first dose of study treatment [ie, primary analysis data cutoff date]).

Subjects will be followed for AEs for 28 days after the last treatment administration. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered *on treatment* until they discontinue the 2nd drug.

Concomitant Drug/Therapy

Subjects will be instructed not to take any additional medications during the course of the study without prior consultation with the treating physician. At each visit, the subject will be asked about any new medications she is taking or has taken after the start of the study drug.

Permitted Concomitant Medications:

No routine prophylactic antiemetic is required. However, the use of palonosetron, prochlorperazine, promethazine, and cyclizine for management of nausea and vomiting is allowed. The use of ondansetron and granisetron is not permitted because of their potential to prolong QT interval.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Growth factors: Prophylactic use of GCSF is not allowed from Cycle 1 Day 9 to Cycle 2 Day 8. Subjects receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pretreatment doses. Following initiation of study treatment, the use of erythropoietic and granulocyte growth factors in accordance with local practice or American Society of Clinical Oncology guidelines may be implemented at the discretion of the treating physician.
- Bisphosphonate use, as recommended according to practice guidelines as long as the subject has been on a stable dose for >30 days prior to study enrollment
- RANKL inhibitor use, as recommended according to practice guidelines, as long as the subject has been on a stable dose >30 days prior to study enrollment
- Anticoagulation with warfarin and derivatives will not be permitted. Should a thrombotic event occur while the subject is receiving treatment, the subject may continue, but low molecular weight heparin, dabigatran, or edoxaban will be the preferred treatment.
- Subjects who develop hyperglycemia during the study should be treated as determined by the treating clinician, according to the national diabetes management guidelines.

Other medications considered necessary for the subject's safety and well-being may be given at the discretion of the investigator with the exception of those listed below.

Prohibited Concomitant Medications

The following treatments are prohibited while on this study:

- No other investigational therapy should be given to subjects. No anticancer agents other than the study medications should be given to subjects. If such agents are required for a subject, then the subject must first be withdrawn from the study.
- In vitro, H3B-6545 is a reversible and time-dependent inhibitor of CYP2C8, 2C9, 2C19, and CYP3A4, as well as an inhibitor of the BCRP, multidrug and toxin extrusion transporter (MATE)1, MATE2-K, organic anion transporting polypeptide (OATP)1B1, and P-gp mediated transport. Drugs with narrow therapeutic index and known to be metabolized by CYP2Cs or CYP3A4 are not permitted because of the inherent potential

risk of either reduced activity or enhanced toxicity of the respective concomitant medication (and/or inhibition of P-gp). Medications that are strong inducers or inhibitors of CYP3A or P-gp should also be avoided since H3B-6545 is a substrate of P-gp and mainly metabolized by CYP3A4, followed by 3A5 and 2C8, and palbociclib is also mainly metabolized by CYP3A. For the most updated information, visit the following Web address: http://medicine.iupui.edu/clinpharm/ddis/.

- Because of a potential drug-drug interaction (DDI), BCRP substrates with narrow therapeutic index are not permitted because H3B-6545 is an inhibitor of BCRP (but not a substrate)
- If, after a subject has been enrolled, she requires the concomitant use of any of the medications that may cause QTc interval prolongation, then H3B-6545 must be held while the subject receives the concomitant medication. Resumption of treatment with H3B-6545 may be considered following discontinuation and washout (at least 5 half-lives) of the concomitant medication if the subject has not progressed and is agreed upon with the sponsor. Excluded medications that may cause QTc interval prolongation are also listed and updated at the following Web address: http://crediblemeds.org.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Subjects should stop using these herbal medications 7 days prior to the first dose of the study drug.
- Nutritional supplements, juice, other foods, or beverages that may affect the various drug-metabolizing enzymes and transporters (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages) are not allowed for 1 week before and throughout the study.
- Systemic corticosteroids are not allowed during the study. Note: The following uses of corticosteroids are permitted: single doses, topical applications (eg, for rash), inhaled sprays (eg, for obstructive airway diseases), eye drops, or local injections (eg, intra-articular). Short courses of systemic corticosteroids may be considered in consultation with the medical monitor.
- Use of short course palliative radiotherapy for symptomatic isolated bone metastases may be allowed following discussion with sponsor.

Assessments

Efficacy Assessments

Tumor assessments will be performed according to RECIST 1.1. Investigator-determined response assessments will be performed at each assessment timepoint and entered onto the case report form. Tumor assessments (computed tomography [CT] chest with IV contrast, and CT (oral and IV contrast) or MRI (IV contrast) of the abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Screening/Baseline period (Day -21 to Cycle 1 Day 1). If imaging with contrast, as requested in above, is contraindicated, imaging without contrast should be performed and reason for contraindication should be captured in the source documents.

Tumor assessments will be performed at post-baseline timepoints (every 8 weeks (±7 days) after Cycle 1 Day 1, or as indicated if disease progression is suspected clinically) using the same imaging modality (eg, contrast-enhanced CT, MRI scan) and under the same operating conditions as the Screening/Baseline scans.

A brain scan (CT with contrast or MRI [pre- and post-gadolinium]) will be performed at Screening, and as clinically indicated to assess potential for CNS disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment timepoints. For all subjects, a follow-up brain scan must be performed to confirm CR within 1 week following response confirmation, or if clinically indicated.

A bone scan using whole body bone MRI, ^{99}m-technetium based bone scans, or ^{18}F-sodium fluoride positron emission tomography will be performed during screening to establish a baseline (a historical bone scan performed within 6 weeks before Cycle 1 Day 1 is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

Tumor assessments will be performed at Screening and every 8 weeks (±7 days) after Cycle 1 Day 1 (ie, 8, 16, 24 weeks) or as indicated if disease progression is suspected clinically.

All responses must be confirmed no less than 28 days following the initial assessment of response. In order for stable disease to be considered the best overall response, it must occur ≥7 weeks following the first dose of study drug.

Subjects who discontinue study treatment without disease progression will continue to have tumor assessments (recorded up to the data cutoff date for the primary analysis) as per the Schedule of Assessments until disease progression, death, or initiation of another anticancer therapy, whichever occurs first, unless the study is terminated.

Pharmacokinetic Assessments

In dose escalation:

- On Cycle 1 Day 8, PK (palbociclib) blood samples to determine plasma concentrations of palbociclib will be collected at predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.
- On Cycle 1 Day 21, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose.
- On Cycle 1 Day 28, PK (H3B-6545) blood samples to determine plasma concentrations of H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose.
- During the treatment phase, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until end of treatment (EOT) or data cutoff date for the primary analysis, whichever is earlier.

In dose expansion:

- On Cycle 1 Day 21, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.
- During the treatment phase, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until progression.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

In dose escalation and expansion:

- At baseline (during screening), pretreatment fresh biopsies or archival tumor tissue (the tumor sample must have been collected after the most recent progression or recurrence) will be obtained from all subjects. If a subject consents to collection of fresh baseline biopsy, it may be acquired any time during the Screening period, before administration of the 1st dose of study drug on Cycle 1 Day 1. If collection of a biopsy during the screening period poses disproportionate risk to subject's safety, the reason for the contraindication must be documented in source at site. Once documentation detailing risk is captured in the site records, subject may continue screening and if all I/E criteria are met, subject may be enrolled and treated.
- At baseline, Cycle 1 Day 1, Cycle 1 Day 21, Cycle 3 Day 1, and every 8 weeks thereafter (coinciding with CT/MRI tumor assessments schedule until radiological progression), and at EOT (if different from date of progression), whole blood samples for mutation characterization from cell-free DNA (cfDNA) will be collected. Biomarker sample collection will end at the time of the primary analysis data cutoff date.

Safety Assessments

Safety assessments will consist of monitoring and recording the following:

- Physical examination
- ECOG performance status
- Height, weight, and vital signs
- 12-lead ECGs
- ECHO, MUGA scan
- Laboratory assessments including but not limited to hematology, biochemistry, and lipid panel

Bioanalytical Methods

Plasma concentrations of H3B-6545 and palbociclib will be determined using validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods. If appropriate, assessment of plasma concentration for any metabolites of H3B-6545 may be explored.

Statistical Methods

Primary Endpoint

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

Secondary Endpoints

- AEs and serious adverse events (SAEs) as well as changes in clinical laboratory values, vital sign measurements and ECG parameters.
- Standard primary PK parameters including, but not limited to, the area under the plasma concentration-time curve from timepoint 0 through the last measurable point (AUC_{0-t}), C_{max}, time of the maximum observed plasma concentration (T_{max}), C_{24}, and ratio of the DDI effect
- ORR, defined as the proportion of subjects achieving a best overall response of confirmed partial or CR (PR+CR)
- DoR, defined as the time from the date of the 1st documented CR/PR until the 1st documentation of disease progression or death, whichever comes first
- CBR, defined as the proportion of subjects achieving a best overall response of confirmed partial or CR, or durable stable disease (duration is at least 23 weeks)
- PFS, defined as the time from the 1st dose date to the date of the 1st documentation of disease progression or death (whichever occurs 1st)
- OS, defined as the time from 1st dose date to the date of death from any cause

Analysis Sets

- *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.
- *Full Analysis Set*: which will consist of all subjects who receive at least 1 dose of study drug.
- *Dose Evaluable Set*: which will consist of all subjects who were evaluable for DLT in Phase 1b. This will be the analysis set for DLT results.
- *Response-Evaluable Set*: 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 postbaseline tumor assessment. This will be the primary analysis set for efficacy evaluations.
- *Pharmacokinetic Analysis Set*: which will consist of subjects who received at least 1 dose of study drug and all valid plasma concentrations (at least 3 valid concentrations for noncompartmental analysis).

Efficacy Analyses

All efficacy parameters will be summarized descriptively for the Response-Evaluable Set and Full Analysis Set. ORR and CBR will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson. DoR will be calculated for subjects achieving a best overall response of confirmed PR+CR. For DoR, PFS, and OS, medians will be calculated using Kaplan-Meier estimates. DoR, PFS, and OS will be reported in both summary tables and plotted with Kaplan-Meier curve.

Pharmacokinetic Analyses

The plasma concentrations of palbociclib and H3B-6545 will be presented by dose level and day, as the number of subjects with data, geometric mean, mean, standard deviation (SD), median, minimum, and maximum values by nominal sampling timepoint. The PK parameters will include, as applicable, C_{max} (T_{max}), AUC_{0-24} (AUC from zero time to 24 hours), AUC_{0-t} (AUC from zero time to last measurable concentration), AUC_{0-inf} (AUC from zero time to infinity), percentage of AUC that is due to extrapolation from the last measurable concentration to infinity ($\%AUC_{Extrap}$), apparent terminal disposition rate constant (λ_z), apparent plasma terminal elimination half-life, apparent total plasma clearance (CL/F), and apparent volume of distribution (V/F).

The palbociclib and H3B-6545 PK parameters will be tabulated per dose level and day, with the number of measurements, number of non-missing data, mean, SD, median, minimum, maximum, geometric mean, and coefficient of variation (CV%; based on untransformed data).

The DDI effect on each other at steady state will be calculated as summarized appropriately (refer to Section 9.4.7.1).

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, PR, 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 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 will be reported separately.

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 using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include

treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and 12-lead ECG results.

Safety will be assessed through the analysis of the reported incidence of TEAEs. The AEs will be coded using the Medical Dictionary for Regulatory Activities, and summarized using system organ class and preferred term. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum National Cancer Institute CTCAE v5.0 grade, and AEs related to study treatment will also be presented by dose level.

Other safety endpoints, including laboratory results, vital signs, and ECG findings, will be summarized for all subjects in the Safety Analysis Set.

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.

Sample Size Rationale

Depending on the dose levels to be studied in the dose escalation part, 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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BCRP	breast cancer resistance protein
BP	blood pressure
CBC	complete blood cell (count)
CBR	clinical benefit rate
cfDNA	cell-free DNA
CL/F	apparent total body clearance following oral administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associates
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment

ER	estrogen receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor-2
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	institutional review board
IV	intravenous
LVEF	left ventricular ejection fraction
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple-gated acquisition
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	preferred term
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANKL	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time of maximum observed plasma concentration
ULN	upper limit of normal
WHO DD	World Health Organization Drug Dictionary

4 ETHICS

4.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRA(s)], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

Where appropriate, at the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 (R2) Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products,

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.

4.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or guardian, in accordance with applicable professional standards and local laws/regulations or legally acceptable representative, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally (PO) consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the screening visit before any study-specific procedures are performed. No subject can enter the study before her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

5 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai, Inc. at approximately 7 investigational site(s) globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File provided to each site.

6 STUDY REGISTRATION

The subject must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, and the potential benefits, alternatives, side effects, risks, and discomforts. Human protection committee (IRB/Independent Ethics Committee [IEC]) approval of this protocol and consent form is required. Eligible subjects who wish to participate in the study will be enrolled into the study.

In Phase 1 of the study, the Sponsor or designee will notify sites via email when a new Dose Level/Cohort is opened and an enrollment slot(s) becomes available. As soon as a potential subject has been identified following the slot availability announcement, sites will notify the Sponsor or designee via email. Sponsor or designee will reply to verify an available slot and reserve the slot for the subject. Upon receipt of confirmation, sites will have 5 business days to consent the identified subject. If a subject is not consented within 5 business days, the slot will open to all sites for enrollment. A patient is enrolled once the approved enrollment packet is returned to the site in ePIP.

The Sponsor or designee will also communicate to all sites via email when a cohort has been fully reserved and screening is closed. This communication may also include language that describes any opportunity for additional screening should a subject screen-fail and/or meet replacement criteria.

Once a site receives confirmation of successful slot reservation, the subject may be consented, and screening procedures may begin. All screening procedures must be completed as outlined in the protocol, and the PI must assess and confirm eligibility of the subject prior to requesting enrollment. Once eligibility is confirmed by the PI and Sponsor or designee, subject registration and dose level assignment will be performed by the Sponsor or designee. The Sponsor or designee will document the subject identification number, dose level, and date of enrollment on the registration form, and will send the completed form back to the site as soon as possible, no later than 24 hours following the registration request.

All subject data collected in the study will be stored under this number. Only the investigator will be able to link the subject's study data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

7 INTRODUCTION

This is an open-label multicenter Phase 1b dose escalation and dose expansion study to evaluate the safety and tolerability of oral H3B-6545 (300 or 450 mg) in combination with palbociclib. The primary objective of the study is to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) 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.

7.1 Compound Overview

Current treatment for most women with advanced ER+ HER2– breast cancer is combination of endocrine therapy (aromatase inhibitors, or fulvestrant) and CDK4/6 inhibitor, eg, palbociclib. The use of CDK inhibitors has dramatically improved clinical outcome in this group of patients (Finn, et al., 2016; Hortobagyi, et al., 2018; Turner, et al., 2018). However, nearly all patients will eventually relapse and therapy for refractory/recurrent disease is suboptimal. Additional improvements in outcome will require novel agents in the frontline setting. H3B-6545 is a novel selective ER covalent antagonist with promising activity as a monotherapy in the nonclinical setting (Smith, et al., 2017). Combination with palbociclib further improves efficacy over single treatments alone in multiple patient-derived human breast cancer xenograft models supporting this combination strategy (data on file).

H3B-6545 is currently in Phase 1/2 clinical trial as a monotherapy in women with advanced metastatic ER+ HER2– breast cancer. Based on available safety and efficacy data from the current Phase 1/2 study of H3B-6545 in heavily pretreated women with ER+ HER2– breast cancer, the drug showed a promising level of activity and a tolerable safety profile (Hamilton, et al., 2019).

Palbociclib, an oral inhibitor of CDK4 and CDK6, has shown activity in metastatic disease settings when combined with endocrine therapy (aromatase inhibitors and fulvestrant) leading to significant improvements in progression-free survival (PFS), suggesting that combination therapy delays the onset of resistance in patients receiving endocrine therapy (Finn, et al., 2016; Turner, et al., 2018). Consistent with this, we show H3B-6545, a selective ER covalent antagonist that covalently engages with ERa, in combination with palbociclib significantly improves efficacy over single-agent treatments in multiple patient-derived human breast cancer xenograft models in female mice.

7.2 Clinical Experience

7.2.1 H3B-6545

As of 15 Sep 2019, 57 subjects were enrolled in the Phase 1/2 Study H3B-6545-A001-101; 47 subjects in the Phase 1 part of the trial and 10 subjects in the Phase 2 part of the trial. The Phase 1 part of the trial evaluated doses ranging from 100 to 600 mg once daily (QD) PO and the dose of 450 mg daily was selected as the RP2D. Median age was 61 years (range: 31 to 81 years), and the median prior therapy for metastatic disease was 3 (range: 1 to 8), with 49% of the subjects receiving at least 4 prior therapies. Prior CDK4/6i, fulvestrant, and chemotherapy were received by 88%, 67%, and 74% of the subjects, respectively. The most common non-AEs are presented in Table 1.

Table 1 Adverse Events, Irrespective of Causality

	100 – 300 mg (N=29)			450 mg (N=21)		
Adverse Event	G2	G3	G4	G2	G3	G4
Neutropenia	0	0	0	0	0	0
Thrombocytopenia	0	3	0	0	0	0
Anemia	14	7	0	14	5	0
ALT	0	3	0	10	0	0
AST	3	10	0	10	0	0
Serum bilirubin	0	3	1	5	0	0
Serum creatinine	3	0	0	0	0	0
Nausea	7	0	0	5	0	0
Vomiting	3	0	0	0	0	0
Diarrhea	7	0	0	5	5	0
Fatigue	14	0	0	5	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; G = grade.

Sinus bradycardia, defined as heart rate less than 60 beats per minute, was observed in approximately 29% of the subjects (Table 2).

Table 2 Sinus Bradycardia

Grade	100 – 300 mg (N=29) n (%)	450 mg (N=21) n (%)
1 (asymptomatic)	10 (34)	5 (24)
2 (symptomatic, no intervention required)	0	1 (5)

No Grade 3 or 4 events were observed. Within the range of doses tested, sinus bradycardia did not seem to be dose related.

Subjects were considered eligible if their QT interval corrected for heart rate using Fridericia's formula (QTcF) was ≤450 ms. Two subjects experienced a QTcF of ≥500 ms, with more than 60 ms of change relative to baseline.

As of the cutoff date, 50 subjects were evaluable for response. Partial responses from 3 subjects were reported (6%), and clinical benefit rate (CBR) (complete response [CR], partial response [PR], or stable disease lasting for ≥23 weeks) was observed in 16 subjects (32%). Median PFS was 5.3 months.

These safety and efficacy data are supportive of further development of H3B-6545 in ER+ HER2– subjects, both as monotherapy and in combination with targeted therapy.

7.2.2 Palbociclib

Palbociclib is a CDK4/6i indicated with letrozole in the primary management of patients with HR+ HER2– advanced breast cancer. The starting dose of palbociclib is 125 mg PO QD on Days 1 to 21 of a 28-day cycle. The most common toxicities are cytopenias, fatigue, nausea, alopecia, and stomatitis.

The toxicity profiles of H3B-6545 and palbociclib suggest that a combination of these drugs is feasible. The potential drug-drug interaction (DDI) between H3B-6545 and palbociclib is discussed in Section 9.7.

7.3 Study Rationale

The proposed study aims to identify the recommended doses of the combination of palbociclib and H3B-6545 and to characterize the safety and toxicity of this combination. Further development of such combination could provide an additional option for the first-line and, potentially, adjuvant treatments of women with ER+ HER2– breast cancer.

In this trial, women with ER+ HER2– advanced breast cancer will be treated with a combination of palbociclib and H3B-6545. During Cycle 1, treatment will consist of palbociclib PO on Days 1 to 21 and H3B-6545 PO on Days 9 to 28. This will allow for the PK profile of the agents to be studied at the following timepoints: Day 8 (palbociclib alone), Day 21 (combination), and Day 28 (H3B-6545 alone). For all subsequent cycles, treatment with both agents will be on a 28-day schedule, with palbociclib being given on Days 1 to 21 and H3B-6545 on Days 1 to 28.

8 STUDY OBJECTIVES

8.1 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 MTD and/or the RP2D of this combination in women with advanced or metastatic ER+ HER2– breast cancer.

8.2 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), CBR (CR, PR, or stable disease ≥23 weeks) PFS, and overall survival (OS)

8.3 Exploratory Objective

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

9 INVESTIGATIONAL PLAN

9.1 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). H3B-6545 will be administered at the assigned dose (PO, QD), in an open-label fashion, for 28-day cycles. During each cycle, palbociclib will be administered at the assigned dose (PO, QD) for the first 21 days of each cycle, in an open-label fashion.

The dose escalation part of the study will accrue approximately 12 to 24 subjects. Total sample size will be determined based on the number of dose-limiting toxicities (DLTs) observed and the number of dose levels (cohorts) studied. The dose expansion phase of the study will enroll a planned 12 additional subjects at the RP2D. Therefore, the study is expected to enroll approximately 24 to 36 subjects. Assuming a 15% screen failure rate, the number of screened subjects is estimated to be 28 to 41.

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.

Subjects who are tolerating therapy and are without progressive disease may receive treatment until progression.

The dose escalation part of the study will determine the MTD and/or the RP2D of H3B-6545 in combination with palbociclib. Each cohort will consist of 6 DLT-evaluable subjects to ensure sufficient safety and PK data are obtained prior to dose escalation. A cycle of treatment will be 28 days.

Due to the potential for screen failures and/or a subject discontinuing treatment before completion of the cohort DLT assessment window (non-evaluable for DLT assessment), up to 8 slots will be opened for screening in order to obtain 6 DLT-evaluable subjects (See Section 9.1). In addition, subjects considered screen failures or unevaluable for DLT will be replaced.

Once 6 subjects have been dosed at the current cohort dose level, any additional subjects in screening will be allocated to one of the following cohorts for enrollment:

- The current cohort so that the total number of DLT-evaluable subjects is maintained at 6, if any of the 6 already dosed subjects becomes non-evaluable for DLT;
- A lower dose cohort which has already been deemed safe per dose escalation meeting, if none of the 6 already dosed subjects becomes non-evaluable for DLT in the cohort currently under evaluation; the additional subject(s) will not contribute to DLT evaluation of the lower dose cohort, but will contribute to the overall safety evaluation.
- The next cohort to be opened to enrollment including the expansion cohort if the RP2D has been reached and the expansion phase is open to enrollment.

Sponsor approval of any enrollment scenario not described above must take place prior to screened subject enrollment.

In the 1st cycle, palbociclib will be administered PO QD on Days 1 to 21 and H3B-6545 will be 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.

A maximum of 4 dose levels are planned, with palbociclib escalated no higher than 125 mg QD and H3B-6545 escalated no higher than 450 mg QD (RP2D); see dose escalation in Table 3.

Table 3 Dose Escalation

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

DLT = dose limiting toxicity; QD = once daily.

Subjects will be assigned to a dose level in the order of study entry. DLTs will be assessed during the first 28 days starting from the 1st day of adding H3B-6545 to palbociclib (Cycle 1 Day 9 to Cycle 2 Day 8). Subjects who do not receive at least 75% of the scheduled therapy

from Cycle 1 Day 9 to Cycle 2 Day 8, for reasons other than toxicity, will not be considered evaluable for DLT assessment and will be replaced. Disease progression and AEs deemed related to disease progression will not be considered DLTs.

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 evaluable 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.

DLT is based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). DLT refers to toxicities experienced by subjects enrolled to the dose escalation portion of the trial during the first 2 cycles of treatment, which are at least possibly related to the study drug. A DLT will be defined as indicated in Table 4.

Table 4 Definition of Dose-Limiting Toxicity

Toxicity	Criteria[a]
Hematology	- Febrile neutropenia (ANC $<1\times10^9$/L and fever ≥38.5 ° C) - Grade 4 neutropenia that does not resolve to Grade ≤2 (ANC $\geq1\times10^9$/L) within 7 days; use of GM-CSF is allowed - Grade 4 thrombocytopenia ($<25.0\times10^9$/L) - Grade 3 thrombocytopenia ($25.0 – 50.0\times10^9$/L) lasting more than 7 days or associated with clinically significant bleeding
Vomiting	- CTCAE Grade 4 vomiting - Grade 3 vomiting lasting >72 hours despite optimal antiemetic treatment
Diarrhea	- CTCAE Grade 4 diarrhea - Grade 3 diarrhea lasting >72 hours despite optimal antidiarrheal treatment
Electrolytes abnormality	- Grade 4 - Grade 3 lasting for more than 24 hours Note: Grade 3 that lasts <24 hours and resolves spontaneously or responds to conventional medical interventions is not considered a DLT.
Renal	- Grade 3 or 4 serum creatinine
Hepatic	- Grade 3 or 4 bilirubin increase - ALT or AST >8 × ULN

	- In absence of liver metastases at baseline and in absence of clinical or radiological evidence of biliary obstruction: ALT or AST >3 × ULN, in conjunction with total bilirubin >2 ×ULN
Biochemistry	- Grade 4 - Grade 3 lasting more than 7 days, unless considered not clinically significant as per the discretion of the investigator
Any other non-hematologic AE	Grade 4 Grade 3 (except diarrhea, rash, nausea, or vomiting lasting ≤72 hours) Any drug-related intolerable Grade 2 toxicity (other than hematological AEs) leading to administration of <75% of the dose during the DLT observation period

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; GM-CSF = granulocyte–macrophage colony-stimulating factor; ULN = upper limit of normal.

a. Laboratory values that meet criteria listed in this table should be repeated and confirmed within 24 hours of the initial results being reported.

Intrasubject dose escalation: Once a subject has completed Cycle 3 at her assigned dose level of drug, intrasubject dose escalation will be allowed. No more than 2 dose escalations are allowed for any subject. Only subjects whose conditions have not progressed on treatment and did not have a dose reduction of either palbociclib or H3B-6545 because of AEs can escalate to the highest dose level that has completed DLT assessment and has been shown to be safe (no more than 1 DLT in 6 subjects). Subjects on the intrasubject dose escalation will ***not*** be included in the DLT analysis at the higher dose level.

Dose expansion: 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.

AEs will be managed by treatment interruption, dose reduction, and/or treatment discontinuation in accordance with the dose modification instructions outlined in the protocol. Treatment will continue until disease progression, development of unacceptable toxicity, or withdrawal of consent.

The data cutoff date for the primary analysis will be approximately 6 months after the last subject receives their first dose of study treatment. The end of study will be the last assessment for the last subject (eg, the last assessment for the last subject in the Extension Phase).

An overview of the study design and the decision rules for selection of the RP2D is presented in Figure 1.

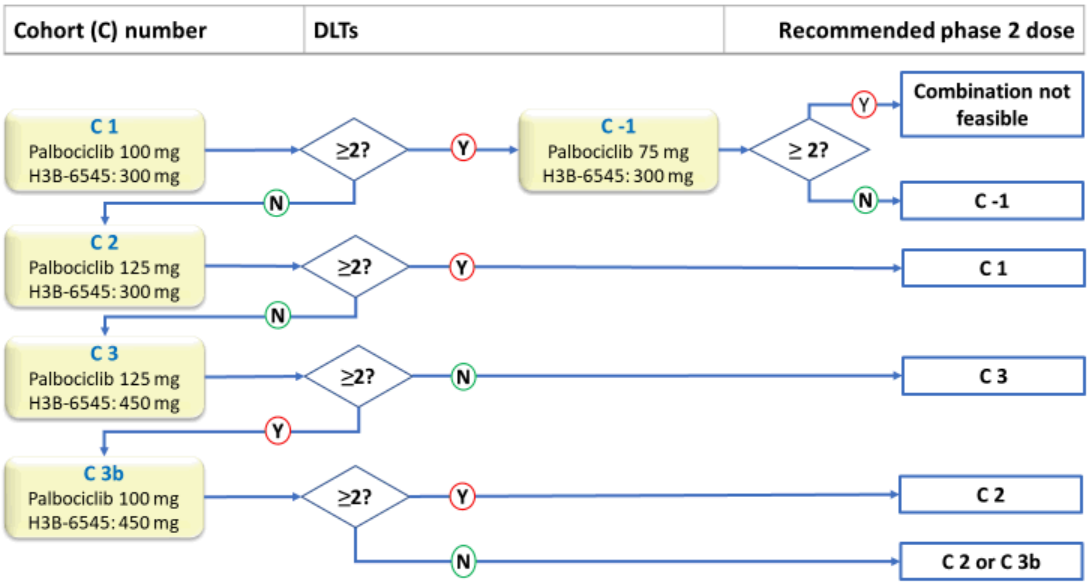

Figure 1 Study Design and Selection of the Recommended Phase 2 Dose

DLT = dose-limiting toxicity; Y = yes; N = no.

9.1.1 Pretreatment Phase

The Pretreatment Phase will last for 3 weeks (from the date of consent signature to the date of first study drug administration) and will include a Screening Period.

Screening will occur between Day –21 and Day 1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 4.3.

Subjects who complete the Screening Period as outlined in Table 8 and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will extend from the start of the first study drug administration and continue until disease progression, development of unacceptable toxicity, or withdrawal of consent.

Treatment cycles will begin with the first dose of palbociclib in Cycle 1 administered PO 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.

9.1.3 Follow-Up Phase

The follow-up phase will extend from treatment discontinuation until the End of Study. All subjects will be followed for survival approximately every 3 months for up to 6 months after the last subject receives their first dose of study treatment). Survival follow-up will not be done in the Extension Phase.

Subjects will be followed for AEs for 28 days after the last treatment administration. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered *on treatment* until they discontinue the 2nd drug.

The cutoff date for the primary analysis will be approximately 6 months after the last subject receives their first dose of study treatment. All subjects who are still on study treatment at that time will enter the Extension Phase.

In the Extension Phase, subjects still on study treatment will continue to receive study drug in 28-day cycles until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, or discontinuation of study by the sponsor. Tumor assessments will be performed according to the local standard of care, but no less than every 12 weeks. The Schedule of Assessments for the Extension Phase will only collect safety and dosing information (Table 9). The End of Treatment (EOT) Visit assessment will occur within 28 (+7 days) days after the final dose of study treatment. All AEs/SAEs will be captured up to 28 days (+7 days) after the last dose of study drug.

If a subject becomes unavailable for follow-up (eg, misses scheduled assessment, telephone contact), the investigator or designee will make every attempt to contact the subject to determine her status. All attempts at contact will be recorded in the subject's medical notes. Subjects will only be deemed lost to follow-up:

- After a minimum of 3 attempted contacts (eg, telephone, letter) with the subject, the subject's family, or the primary care (family) physician, at least 4 weeks apart. The last attempt at contact must occur no earlier than 3 months after the subject's last successful contact.
- If the last attempt at contact is unsuccessful, the site should write a letter with certified proof of posting or regional equivalent method to the subject, subject's family, or the primary care (family) physician to request information on the subject's status.

Subjects who discontinue trial therapy for any reason other than documented radiological progression, entrance into the Extension Phase or withdrawal of consent must still follow all safety assessments until the Safety Follow-up Visit (28 days after last treatment administration) and efficacy assessments (every 8 weeks ± 1 week) until documented disease progression or starting another anticancer therapy.

9.2 Discussion of Study Design, Including Choice of Control Groups

The goals of Phase 1 oncology studies include estimation of the initial safety and tolerability of a study drug, establishment of an MTD, and determination of a recommended range of doses for evaluation in future clinical studies, based on PK and PD effects (Dillman and Koziol, 1992; Gatsonis and Greenhouse, 1992; ICH E8, 1997; Ahn, 1998); the primary objectives of the current study are consistent with those typical of Phase 1 oncology studies.

During the dose escalation phase of the study, 6 evaluable subjects will be enrolled at each cohort in order to increase confidence in the safety assessment of this combination at different dose levels. An integrated evaluation of safety and tolerability will be used to select the RP2D schedule to be implemented before the dose expansion phase.

Preliminary assessment of activity or potential therapeutic benefit may be a secondary objective of Phase 1 studies (ICH E8, 1997). Consistent with this premise, a secondary objective is to evaluate the potential antitumor activity of the combination of H3B-6545 and palbociclib.

9.3 Selection of Study Population

Approximately 24 to 36 subjects will be enrolled at approximately 7 centers globally. The dose escalation phase of the study will accrue approximately 12 to 24 subjects. The dose expansion phase of the study will enroll a planned 12 additional subjects at the RP2D. Assuming a 15% screen failure rate, the number of screened subjects is estimated to be 28 to 41. The study will include women with advanced or metastatic ER+ HER2– breast cancer.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

1. Subjects must meet all of the following criteria to be included in this study:
2. Subject has signed ICF before any study-related activities and according to local guidelines.
3. Female, aged ≥18 years, at the time of informed consent

   Subject has histopathologically or cytologically confirmed ER+ HER2– locally advanced, recurrent, or metastatic breast cancer, as per local laboratory
4. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Subjects enrolling to the study who do not have measurable disease at baseline per RECIST 1.1 guidelines may be enrolled if they have at least 1 mainly lytic bone lesion, provided that the lesion has not been irradiated or exhibits demonstrable progression since irradiation.
5. Prior therapy in the advanced or metastatic setting:

- Dose escalation: 2 or more prior hormonal therapies. Subjects may have received up to 1 prior chemotherapy regimen and up to 1 prior CDK4/6 inhibitor.

- Dose expansion: Up to 2 prior endocrine therapies and up to 1 prior chemotherapy regimen but may not have received a prior CDK4/6 inhibitor.

  Note: If the patient was enrolled within 12 months of the end of adjuvant therapy, the adjuvant therapy will also be counted.

  Note: Subjects must have documented progression while on or after the most recent therapy.

6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2).
7. Life expectancy >12 weeks, as per investigator's best assessment, during the Screening phase.
8. Subject has adequate bone marrow and organ function, as defined by the following laboratory values:
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   b. Platelets $\geq 100 \times 10^9$/L
   c. Hemoglobin ≥9.0 g/dL (may have been transfused)
   d. Potassium, sodium, calcium (corrected for serum albumin), and magnesium CTCAE ≤Grade 1
   e. International normalized ratio ≤1.5
   f. Serum creatinine ≤1.5× upper limit of normal (ULN)
   g. Serum albumin ≥3.0 g/dL (≥30 g/L)
   h. In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0×ULN. If the patient has liver metastases, ALT and AST ≤5×ULN
   i. Total serum bilirubin <1.5×ULN except for patients with Gilbert's syndrome who may be included if the total serum bilirubin is ≤3.0×ULN or direct bilirubin ≤1.5× ULN
9. Willingness and ability to comply with study and follow-up procedures.
10. No concurrent antineoplastic therapy. Use of bone-modifying agents, including bisphosphonate and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors is permitted.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Known central nervous system (CNS) metastases, including meningeal carcinomatosis. Brain or subdural metastases are not allowable, unless the patient has completed local therapy and has discontinued the use of corticosteroids for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.

2. Subject has a concurrent malignancy or malignancy within 3 years of enrollment, with the exception for basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has completed curative therapy. Known human immunodeficiency virus infection.
3. Uncontrolled significant active infections. Note: subjects with diagnosis of hepatitis B virus and/or hepatitis C virus infection must have undetectable viral load during screening (Appendix 3).
4. Major surgery or other locoregional treatment within 4 weeks before the 1st dose of study drug.
5. Inability to take oral medication or presence of malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of H3B-6545. Palbociclib contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
6. Currently participating in another clinical study or has received other investigational drugs within 28 days.
7. Active cardiac disease or a history of cardiac dysfunction, including any of the following:
   a. History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry
   b. History of documented congestive heart failure (New York Heart Association functional classification III or IV)
   c. Documented cardiomyopathy
   d. Subject has a left ventricular ejection fraction (LVEF) <50% as determined by multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO)
   e. History of any cardiac arrhythmias in the previous 12 months
   f. A prolonged QTcF >450 ms as demonstrated by a repeated electrocardiogram (ECG); a history of risk factors for Torsade de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome) or the use of concomitant medications that prolonged the QTcF interval
   g. Subject has resting pulse rate <60 bpm
8. Females of childbearing potential who:

   Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:

   a. Double-barrier contraception (considered acceptable method but not highly effective)
   b. Total abstinence (if it is their preferred and usual lifestyle)
   c. An intrauterine device
   d. Have a vasectomized partner with confirmed azoospermia.

   Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days (or 5 times the half-life of the study drug, whichever is longer) after study drug discontinuation.

Note: All females will be considered to be of childbearing potential unless they are postmenopausal (has amenorrhea for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

9. Known intolerance to either study drug or any of the excipients.
10. Subject received in the 7 days prior to the administration of study drug or is currently receiving any of the following medications:
    a. Known strong inducers or inhibitors of cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp)
    b. Medications that have a narrow therapeutic window and are breast cancer resistance protein (BCRP) substrate
    c. Medications that have a known risk to prolong the QT interval or induce Torsades de Pointes
    d. Medications that have a narrow therapeutic window and are predominantly metabolized through CYP2C8, CYP2C9, CYP2C19, or CYP3A4
    e. Herbal preparations/medications; these herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng.
11. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] (or hCG) test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of the study drug.
12. Active interstitial lung disease (ILD) or diagnosis of ILD within the last 12 months
13. Any medical or other condition that, in the opinion of the investigator(s), would preclude the subject's participation in a clinical study.
14. Exposure within the last 14 days to an individual with confirmed or probable COVID-19 or symptoms within the last 14 days or any other reason to consider the subject at potential risk for an acute COVID-19 infection.

    Note: Please consider testing for active COVID-19 infection prior to starting trial therapy according to the institution guidelines.
15. Evidence of ongoing Alcohol or Drug Abuse

9.3.3 Removal of Subjects From Therapy or Assessment

Subjects will continue to receive study treatment until any of the following occur:

- Disease progression

- Development of unacceptable toxicity. In absence of liver metastases at baseline and in absence of clinical or radiological evidence of biliary obstruction: ALT or AST >3 × ULN, in conjunction with total bilirubin >2 ×ULN
- Withdrawal of consent
- Subject request
- Inability to comply with protocol requirements

The reason for treatment discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will discontinue trial therapy but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

During the Follow-Up Period, subjects who have discontinued study treatment without progression will be followed for disease assessments every 8 weeks from the date of the last assessment until the data cutoff date for the primary analysis, or until disease progression is documented or another anticancer therapy is initiated. Subjects will be followed for AEs for 28 days after the last treatment administration. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered *on treatment* until they discontinue the 2nd drug.

All subjects will be followed for survival until death approximately every 3 months for up to 6 months after the last subject receives their first dose of study treatment (ie, primary analysis data cutoff date), except where a subject withdraws consent or the sponsor chooses to halt survival follow-up.

9.4 Treatments

9.4.1 Treatments Administered

H3B-6545 is administered PO. All subjects will take H3B-6545 at their assigned dose (PO, QD), in an open-label fashion, for 28-day cycles. On days that H3B-6545 will be taken with palbociclib, subjects should take H3B-6545 **at the same time** as palbociclib.

Palbociclib is taken PO QD for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

H3B-6545 and palbociclib should be taken with food. Subjects should be encouraged to take their dose at approximately the same time each day and within 30 minutes of completing a meal. H3B-6545 capsules and palbociclib capsules or tablets should be swallowed whole. Capsules or tablets should not be ingested if they are broken, cracked, or otherwise not intact. Dosing should not be repeated if a subject vomits. A dose missed by more than 12 hours should be skipped. The next prescribed dose should be taken at the usual time.

A study-specific pharmacy manual will be provided to each participating institution and will include information for receipt, storage, administration, accountability, and destruction of study supplies and/or investigational products including H3B-6545 and palbociclib.

9.4.2 Identity of Investigational Products

H3B-6545 will be supplied as opaque, hypromellose shell capsules, size 4 containing 50 mg or size 1 containing 150 mg of H3B-6545 drug substance. The composition ratio of the capsule content is the same for both strengths.

Palbociclib will be supplied as 125, 100, and 75 mg capsules or tablets.

9.4.2.1 Chemical Name of H3B-6545

- Test drug code: H3B-6545
- Chemical name:
  Chemical Abstracts Services (CAS): 2-Butenamide, *N,N*-dimethyl-4-[[2-[[5-[(1*Z*)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenyl-1-buten-1-yl]-2-pyridinyl]oxy]ethyl]amino]-,hydrochloride (1:1), (2*E*)-

  CAS registry number: 2052132-51-9

  International Union of Pure and Applied Chemistry: (2*E*)-*N,N*-Dimethyl-4-{[2-({5-[(1Z)-4,4,4-trifluoro-1-(3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl]pyridin-2-yl}oxy)ethyl]amino}but-2-enamide hydrochloride
- Molecular formula: $C_{30}H_{29}F_4N_5O_2 \cdot HCl$
- Molecular weight: 604.05 (567.59, free base)

9.4.2.2 Chemical Name of Palbociclib

- Generic name: palbociclib
- Chemical name: 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
- Molecular formula: $C_{24}H_{29}N_7O_2$
- Molecular weight: 447.54
- Refer to the latest palbociclib (Ibrance®) package insert (Ibrance USPI, 2019)

9.4.2.3 Labeling for Study Drug

H3B-6545 and palbociclib will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

All study drugs must be kept in a secure place under appropriately labeled storage conditions.

Study drugs will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device (such as a calibrated chart recorder) or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

The sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive H3B-6545 in combination with palbociclib. There is no randomization in this study.

The dose escalation phase of the study will determine the MTD and/or the RP2D of H3B-6545 in combination with palbociclib. Each cohort will consist of 6 evaluable subjects to ensure sufficient safety and PK data are obtained prior to dose escalation. A cycle of treatment will be 28 days.

During the 1st cycle, palbociclib will be administered PO QD on Days 1 to 21, and H3B-6545 will be 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.

The dose expansion phase of the study will treat an additional 12 subjects 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.

9.4.4 Selection of Doses in the Study

A maximum of 4 dose levels are planned with palbociclib escalated no higher than 125 mg QD and H3B-6545 escalated no higher than 450 mg QD (RP2D); see dose escalation in Table 3.

9.4.5 Selection and Timing of Dose for Each Subject

All subjects will take H3B-6545 at their assigned dose (PO, QD), in an open-label fashion, for 28-day cycles. On days that H3B-6545 will be taken with palbociclib, subjects should take H3B-6545 at the same time as palbociclib.

Palbociclib is taken PO QD for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

H3B-6545 and palbociclib should be taken with food, and subjects should be encouraged to take their dose at approximately the same time each day and within 30 minutes of completing a meal.

9.4.6 Blinding

This study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Subjects will be instructed not to take any additional medications during the course of the study without prior consultation with the treating physician. At each visit, the subject will be asked about any new medications she is taking or has taken after the start of the study drug.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 28 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with H3B-6545 and/or palbociclib may be continued during the study.

Treatment of complications or AEs or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs) may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) H3B-6545 and/or palbociclib.

Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell counts.

9.4.7.1 Drug-Drug Interactions

Palbociclib is primarily metabolized by CYP3A and sulfotransferase enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A. Please refer to the latest palbociclib (Ibrance) package insert (Ibrance USPI, 2019).

In vitro metabolism studies suggest that H3B-6545 is metabolized mainly by CYP3A4, followed by CYP3A5 and CYP2C8; it is a reversible and time-dependent inhibitor of CYP2C8, 2C9, 2C19, and CYP3A4, and a potential inducer of CYP3A4 at high concentrations potentially achievable at a therapeutic dose.

A DDI between H3B-6545 and palbociclib is mechanistically potential, but the magnitude is not expected to be high due to multiple metabolic pathways for both drugs.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

The following treatments are prohibited while on this study:

- No other investigational therapy should be given to subjects. No anticancer agents other than the study medications should be given to subjects. If such agents are required for a subject, then the subject must first be withdrawn from the study.
- In vitro, H3B-6545 is a reversible and time-dependent inhibitor of CYP2C8, 2C9, 2C19, and CYP3A4, as well as an inhibitor of the BCRP, multidrug and toxin extrusion transporter (MATE)1, MATE2-K, organic anion transporting polypeptide (OATP)1B1, and P-gp mediated transport. Drugs with narrow therapeutic index and known to be metabolized by CYP2Cs or CYP3A4 are not permitted because of the inherent potential risk of either reduced activity or enhanced toxicity of the respective concomitant medication (and/or inhibition of P-gp). Medications that are strong inducers or inhibitors of CYP3A or P-gp should also be avoided since H3B-6545 is a substrate of P-gp and mainly metabolized by CYP3A4, followed by 3A5 and 2C8, and palbociclib is also mainly metabolized CYP3A. For the most updated information, visit the following Web address: http://medicine.iupui.edu/clinpharm/ddis/. Histamine H_2-receptor antagonists.
- Because of a potential DDI, BCRP substrates with narrow therapeutic index are not permitted because H3B-6545 is an inhibitor of BCRP (but not a substrate) (Appendix 1)
- If, after a subject has been enrolled, she requires the concomitant use of any of the medications that may cause QTc interval prolongation, then H3B-6545 must be held while the subject receives the concomitant medication. Resumption of treatment with H3B-6545 may be considered following discontinuation and washout (at least 5 half-lives) of the concomitant medication if the subject has not progressed and is agreed upon with the sponsor. Excluded medications that may cause QTc interval prolongation are also listed and updated at the following Web address: http://crediblemeds.org.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang),

gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. Subjects should stop using these herbal medications 7 days prior to the first dose of the study drug.

- Nutritional supplements, juice, other foods, or beverages that may affect the various drug-metabolizing enzymes and transporters (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages) are not allowed for 1 week before and throughout the study.
- Systemic corticosteroids are not allowed during the study. Note: The following uses of corticosteroids are permitted: single doses, topical applications (eg, for rash), inhaled sprays (eg, for obstructive airway diseases), eye drops, or local injections (eg, intra-articular). Short courses of systemic corticosteroids may be considered in consultation with the medical monitor.
- Use of short course palliative radiotherapy for symptomatic isolated bone metastases may be allowed following discussion with sponsor.

9.4.7.3 Permitted Concomitant Medications

No routine prophylactic antiemetic is required. However, the use of palonosetron, prochlorperazine, promethazine, and cyclizine for management of nausea and vomiting is allowed. The use of ondansetron and granisetron is not permitted because of their potential to prolong QT interval.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Growth factors: Prophylactic use of GCSF is not allowed from Cycle 1 Day 9 to Cycle 2 Day 8. Subjects receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pretreatment doses. Following initiation of study treatment, the use of erythropoietic and granulocyte growth factors in accordance with local practice or ASCO guidelines may be implemented at the discretion of the treating physician.
- Bisphosphonate use, as recommended according to practice guidelines as long as the subject has been on a stable dose for >30 days prior to study enrollment
- RANKL inhibitor use, as recommended according to practice guidelines, as long as the subject has been on a stable dose >30 days prior to study enrollment
- Anticoagulation with warfarin and derivatives will not be permitted. Should a thrombotic event occur while the subject is receiving treatment, the subject may continue, but low-molecular-weight heparin, dabigatran, or edoxaban will be the preferred treatment.
- Subjects who develop hyperglycemia during the study should be treated as determined by the treating clinician, according to the national diabetes management guidelines.

Other medications considered necessary for the subject's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 9.4.7.2.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. A diary will be provided to subjects on Cycle 1 Day 1 to document the date and time of each study drug dose for all treatment cycles as well as the incidence of vomiting following administration. The investigator will review and document treatment compliance for each subject at each visit. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, the initial drug supply will not be sent to the investigator until local regulatory and IRB/IEC approvals are available, and all required forms and documentation have been reviewed by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, or a completed Investigator and Site Information Form
- Financial disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects,

and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Dose Modifications

Neutropenia was the most frequently reported adverse reaction in palbociclib clinical trials, with an incidence of 80% to 83%. A Grade ≥3 decrease in neutrophil counts was reported in 66% of patients receiving palbociclib plus letrozole or fulvestrant. The median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥3 neutropenia was 7 days.

Febrile neutropenia has been reported in 1.8% of patients exposed to palbociclib across studies. Physicians should inform patients to promptly report any episodes of fever.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of palbociclib and/or H3B-6545.

Recommendations for dose reduction, interruption or discontinuation of either drug in the management of adverse reactions are summarized in Table 5 (hematologic toxicities) and

Table 6 (non-hematologic toxicities). Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Two dose reductions of H3B-6545 (450 mg to 300 mg, and then to 150 mg QD) for toxicity will be allowed as per the guidance summarized in Table 5 and Table 6. If persistent toxicity occurs despite 2 dose reductions, the subject will discontinue study treatment.

Two dose reductions for palbociclib (125 mg to 100 mg, and then to 75 mg QD) for toxicity will be allowed (Table 5 and Table 6). If persistent toxicity occurs despite 2 dose reductions, the subject will discontinue study treatment.

Hematologic toxicities

Monitor complete blood cell (CBC) counts prior to the start of palbociclib therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor CBC counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

Table 5 Dose Modifications and Management Recommendation – Hematologic Toxicities

CTCAE Grade	Palbociclib	H3B-6545
Anemia		
Grade 4	Withhold dose until recovery to Grade ≤2; resume drug at next lower dose	Withhold dose until recovery to Grade ≤2; resume drug at next lower dose
Grade 3	• Day 1 of cycle: Withhold drug, repeat complete blood cell count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. • Day 15 of first 2 cycles: Continue palbociclib at current dose to complete cycle and repeat complete blood cell count on Day 22.	Withhold dose until recovery to Grade ≤2; resume drug at next lower dose
Grade 1 or 2	No dose adjustment is required	No dose adjustment is required
All other hematological toxicity		
Grade 4	Withhold dose until recovery to Grade ≤2; resume drug at next lower dose	No dose adjustment is required.
Grade 3	• Day 1 of cycle: Withhold drug, repeat complete blood cell count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose.	No dose adjustment is required.

	• Day 15 of first 2 cycles: Continue palbociclib at current dose to complete cycle and repeat complete blood cell count on Day 22.	
Grade 1 or 2	No dose adjustment is required	No dose adjustment is required
Grade 3 neutropenia with fever ≥38.5 °C and/or infection	Withhold palbociclib until recovery to Grade ≤2; resume at the next lower dose	Withhold dose until fever subsides; resume at the same dose

CTCAE = Common Terminology Criteria for Adverse Events.

a. Laboratory values that meet criteria listed in this table should be repeated and confirmed within 24 hours of the initial results being reported.

b. Subjects who do not receive at least 75% of the dose for reasons other than toxicity (eg, withdrawal of consent, physician decision, lost to follow-up, etc.) will not be considered evaluable for DLT

Nonhematologic Toxicities

Table 6 Dose Modifications and Management Recommendation – Nonhematologic Toxicities

CTCAE Grade	Palbociclib	H3B-6545
Sinus bradycardia		
Grade 1 (asymptomatic) Heart rate ≥40 bpm	No dose adjustment is required	No dose adjustment is required
Grade 1 (asymptomatic) Heart rate <40 bpm	No dose adjustment is required	First occurrence: Withhold drug until heart rate is ≥50 bpm; resume drug at the same dose level Second occurrence: Withhold drug until heart rate is ≥50 bpm; resume drug at the next lower dose
Grade 2 (symptomatic, intervention not indicated; change in medication initiated)	No dose adjustment is required	Withhold drug until (a) symptoms resolve and (b) heart rate is ≥50 bpm; resume drug at the next lower dose
Grade 3 (symptomatic, intervention indicated)	Withhold palbociclib until (a) symptoms resolve and (b) heart rate is ≥50 bpm; resume drug at the next lower dose	Withhold drug until (a) symptoms resolve and (b) heart rate is ≥50 bpm; resume drug at the next lower dose
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Withhold palbociclib until (a) symptoms resolve and (b) heart rate is ≥50 bpm; resume drug at the next lower dose	Discontinue drug
QTcF prolongation		
Grade 1 (average: 450 – 480 ms)	No dose adjustment is required	No dose adjustment is required

Grade 2 (average: 481 – 500 ms)	No dose adjustment is required	No dose adjustment is required Repeat assessment after 1 week; if the average is still between 481 and 500 mg, decrease to the next lower dose
Grade 3 (average: ≥501 ms; >60 ms change from baseline)	Withhold drug until average is <480 ms **and** <60 ms change from baseline; resume at the next lower dose	Withhold drug until average is <480 ms **and** <60 ms change from baseline; resume at the next lower dose
Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Discontinue drug	Discontinue drug
Other		
Grade 1 or 2	No dose adjustment is required	No dose adjustment is required
Grade 3 or 4 (if persisting despite optimal medical care)	Withhold palbociclib until symptoms resolve to Grade ≤2; resume drug at the next lower dose	Withhold drug until symptoms resolve to Grade ≤2; resume drug at the next lower dose

CTCAE = Common Terminology Criteria for Adverse Events; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Monitor subjects for pulmonary symptoms indicative of ILD/pneumonitis (eg, hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the subject. Permanently discontinue palbociclib in subjects with severe ILD or pneumonitis.

Dose modifications for use with strong CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be co-administered a strong CYP3A inhibitor:

- Reduce the palbociclib dose to 75 mg QD
- Reduce the H3B-6545 dose to 150 mg QD

If the strong inhibitor is discontinued, increase the palbociclib and H3B-6545 doses (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

9.6 Study Assessments

9.6.1 Assessments

9.6.1.1 Screening Assessments

The following information will be collected, and procedures will be performed for each subject at screening up to 21 days prior to initiation of treatment:

- Written ICF prior to any other study-related procedures
- Assessment of inclusion/exclusion criteria
- Medical history, including cancer history
- Collection of pretreatment fresh biopsies or archival tumor tissue (the tumor sample must have been collected after the most recent progression or recurrence). If collection of a biopsy during the screening period poses disproportionate risk to subject's safety, the reason for the contraindication must be documented in source at site. Once documentation detailing risk is captured in the site records, subject may continue screening and if all I/E criteria are met, subject may be enrolled and treated.
- Demography
  - Data to be tabulated will include at least demographic features such as sex, age, and race, as well as weight- and disease-specific status and medical history.
- Medical History
  - Medical and surgical history and current medical conditions will be recorded at the Screening Visit. This will include all cancer and cardiac history. All other medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions case report form (CRF).

Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure [BP], respiratory rate, oral temperature). Height will be recorded at the baseline visit only (Table 8).

9.6.1.2 Efficacy Assessments

9.6.1.2.1 Tumor Assessments

Tumor assessments will be performed according to RECIST 1.1. Investigator-determined response assessments will be performed at each assessment timepoint and entered onto the CRF. Tumor assessments (computed tomography [CT] chest with IV contrast, and CT (oral and IV contrast) or magnetic resonance imaging (MRI) (IV contrast) of the abdomen, pelvis, and other known or suspected sites of disease) will be performed during Screening/Baseline period (Day -21 to Cycle 1 Day 1). If imaging with contrast, as requested in above, is contraindicated, imaging without contrast should be performed and reason for contraindication should be captured in the source documents.

Tumor assessments will be performed at postbaseline timepoints (every 8 weeks (±7 days) after Cycle 1 Day 1, or as indicated if disease progression is suspected clinically) using the same imaging modality (eg, contrast-enhanced CT, MRI scan) and under the same operating conditions as the Screening/Baseline scans.

A brain scan (CT with contrast or MRI [pre- and postgadolinium]) will be performed at Screening and as clinically indicated to assess potential for CNS disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment timepoints. For all subjects, a follow-up brain scan must be performed to confirm CR within 1 week following response confirmation or if clinically indicated.

A bone scan using whole body bone MRI, ^{99}m-technetium based bone scans, or ^{18}F-sodium fluoride positron emission tomography will be performed during screening to establish a baseline (a historical bone scan performed within 6 weeks before Cycle 1 Day 1 is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

Tumor assessments will be performed at Screening and every 8 weeks (±7 days) after Cycle 1 Day 1 (ie, 8, 16, 24 weeks) or as indicated if disease progression is suspected clinically.

All responses must be confirmed no less than 28 days following the initial assessment of response. In order for stable disease to be considered the best overall response, it must occur ≥7 weeks following the first dose of study drug.

Subjects who discontinue study treatment without radiological disease progression will continue to have tumor assessments as per the Schedule of Assessments until radiological disease progression, death, or initiation of another anticancer therapy, whichever occurs first, unless the study is terminated.

Refer to Section 9.1.3 and Table 9 for the schedule of tumor assessments in the Extension Phase. Survival follow-up will end 6 months after the last subject completes the first dose of study treatment.

9.6.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.6.1.3.1 PHARMACOKINETIC ASSESSMENTS

In dose escalation:

- On Cycle 1 Day 8, PK (palbociclib) blood samples to determine plasma concentrations of palbociclib will be collected at predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30

minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.

- On Cycle 1 Day 21, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose.
- On Cycle 1 Day 28, PK (H3B-6545) blood samples to determine plasma concentrations of H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose.
- During the treatment phase, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until EOT or data cutoff date for the primary analysis, whichever is earlier.

In dose expansion:

On Cycle 1 Day 21, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.

During the treatment phase, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose in conjunction with each tumor assessment, that is, approximately every 8 weeks until progression.

Blood samples (4 mL for H3B-6545 and 4 mL for palbociclib) will be collected as specified in Table 8. See PK or Laboratory Manual for a description of the collection, handling, and shipping procedures of PK samples.

Blood will also be drawn where possible at the first report of a serious adverse event (SAE) or severe unexpected AE and at its resolution.

9.6.1.3.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

In dose escalation and expansion:

- At baseline (during screening), pretreatment fresh biopsies or archival tumor tissue (the tumor sample must have been collected after the most recent progression or recurrence) will be obtained from all subjects. If a subject consents to collection of fresh baseline biopsy, it may be acquired any time during the Screening period, before administration of the 1st dose of study drug on Cycle 1 Day 1. If collection of a biopsy during the screening period poses disproportionate risk to subject's safety, the reason for the contraindication must be documented in source at site. Once documentation detailing risk is captured in the site records, subject may continue screening and if all I/E criteria are met, subject may be enrolled and treated.

- At baseline, Cycle 1 Day 1, Cycle 1 Day 21, Cycle 3 Day 1, and every 8 weeks thereafter (coinciding with CT/MRI tumor assessment schedule until radiological progression), and at EOT (if different from date of progression), whole blood samples for mutation characterization from cell-free DNA (cfDNA) will be collected. No further sample collection will be done after the data cutoff date for the primary analysis.

Tumor tissue samples and blood samples for PD, PGx, and other biomarker assessments will be collected from all consented study subjects, except where prohibited by regional or local laws. Samples will be collected at designated timepoints as specified in the Schedule of Procedures/Assessments (Table 8). Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Samples may be used for biomarker discovery and/or validation to identify blood or tumor biomarkers that may be useful to predict treatment response (efficacy, PD), PK, and/or safety-related outcomes. Samples may also be used for potential diagnostic development. In addition, biomarkers identified in other clinical studies may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of the study and/or the signals observed in other clinical studies.

Pretreatment fresh biopsies or archival tumor tissue will be collected (if available) from all subjects for the assessment of RNA, mutations, and other genetic alterations or proteins that may be important in the development and progression of cancer.

Whole blood samples will be collected for cfDNA analysis from all subjects. cfDNA isolated from blood plasma samples may be used to explore tumor genetic alterations, including mutations observed in archival tumor samples and mutations that may emerge with drug treatment.

9.6.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v5.0 grades (for both increasing and decreasing severity); regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in Table 8.

The following will be monitored and recorded:

- Physical examination
- ECOG performance status
- Height, weight, and vital signs
- 12-lead ECGs
- ECHO, MUGA scan
- Laboratory assessments (refer to Table 7 and Table 8)

9.6.1.4.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) is(are) H3B-6545 and palbociclib.

The criteria for identifying AEs in this study are as follows:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE, unless the event meets criteria for a serious AE as outlined in Section 9.6.1.4.2. In such cases, the event should be reported as an SAE.
- Any deterioration in non–protocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present before treatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through 28 days after last treatment administration. Refer to Section 9.6.4.2 for the time period after the EOT for SAE collection.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such. *Note: If sinus bradycardia is observed at EOT visit, follow-up ECGs should be performed weekly until heart rate has returned 60 bpm or more or prestudy baseline.*

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered on treatment until they discontinue the 2nd drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Subjects with onset of an AE or deterioration of a preexisting AE during the AE collection period will be followed until resolution to baseline, start of a new anticancer treatment, or death.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 5-point scale according to CTCAE v5.0. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are as follows:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non–study treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	**A causal relationship between the study drug and the AE is a reasonable possibility.**
No (not related)	**A causal relationship between the study drug and the AE is not a reasonable possibility.**

9.6.1.4.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. For example, an isolated laboratory abnormality could be considered to meet the criteria for serious (eg, if the event results in hospitalization or is considered medically significant). Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not

necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. It is based on subject/event outcome or action usually associated with events that pose a threat to a subject's life or vital functions.

For example, nausea, which persists for several hours, may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke, which results in only a limited degree of disability, may be considered only a mild stroke, but it would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF screen and SAEs on the SAE Report Form.

9.6.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 7. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 8) shows the visits and timepoints at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 7 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and total WBC count with 5-part differential
Coagulation	INR, PT, aPTT
Comprehensive metabolic panel	Fasting glucose, calcium, albumin, total protein, electrolytes (sodium, potassium, carbon dioxide, chloride), renal function tests (blood urea/blood urea nitrogen, creatinine), liver function tests (ALP, ALT, AST, bilirubin)
Other	Albumin, CRP, fasting lipase, fasting amylase, lactate dehydrogenase, magnesium, phosphorus, gamma-glutamyl transpeptidase, and thyroid function tests (TSH and free T_4)
Virology	HBV, HCV, HIV
Urine dipstick	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CRP = C-reactive protein; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = International normalized ratio; PT = prothrombin time; RBC = red blood cell; T_4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell.

Central laboratory will be used for PK/PD and biomarker assessments. For all safety assessments (eg, liver and kidney function, blood count), the sites will use local laboratories.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration, and results will be reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.6.1.4.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.6.1.4.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, resting heart rate, BP, respiratory rate, oral temperature) and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 8) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 10 minutes. All BP measurements should be performed on the same arm, preferably by the same person. For subjects with an elevated BP (≥140/90 mmHg), confirmation should be obtained by performing 3 measurements (at least 5 minutes apart) to yield a mean value. Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg should be confirmed by repeat measurements after 1 hour.

9.6.1.4.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 8). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.6.1.4.6 Electrocardiograms

ECG assessments will be performed in triplicate for all study visits where ECGs are required and ECGs should be collected predose on days where PK samples are not collected (Table 8).

Triplicate 12-lead ECG will be performed after the patient has been resting for 10 minutes prior to each timepoint indicated and at unscheduled visits as clinically required. The ECGs should be taken while the patient in a semi-recumbent position. At Screening, triplicate ECGs should be taken approximately 5 minutes apart. On Cycle 1 Day 1, triplicated ECGs should be performed predose. The combined QTcF values will be averaged to provide a single baseline value for each patient. This averaged value will be documented in the ECG section of the CRF. ECG measurements on Cycle 1 Day 8, Cycle 1 Day 21, and Cycle 1 Day 28 should match the PK collection. Data from local safety ECGs should be entered into the clinical database.

In addition, in the event of any alteration or if clinically indicated, additional ECGs and/or cardiac enzyme evaluations should be performed. If sinus bradycardia is observed at EOT visit, follow up ECGs should be performed weekly until heart rate has returned to 60 or more beats per minute or pre-study baseline.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.6.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting the criteria of an SAE, the site must fax or email the SAE report including the ECG report to the Sponsor using the SAE form.

9.6.1.4.7 OTHER SAFETY ASSESSMENTS

A MUGA scan or an ECHO to assess LVEF will be performed at screening, at Cycle 3 Day 1, and if clinically indicated thereafter. MUGA scans should be performed locally in accordance with the institution's standard practice; ECHO should be performed following the protocol provided by the cardiovascular core laboratory. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at Baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

Pregnancy Test

A serum pregnancy test must be performed at Screening for all women of childbearing potential (ie, pre- and perimenopausal subjects). There is no need to repeat the test on Cycle 1 Day 1 if performed within 72 hours. Thereafter, during the study, urine testing should be performed at Day 1 of each cycle or serum testing should be performed to confirm a positive urine testing.

9.6.2 Schedule of Procedures/Assessments

9.6.2.1 Schedule of Procedures/Assessments

Table 8 presents the schedule of procedures/assessments for the dose escalation and dose expansion phases of the study. Table 9 presents the procedures during the Extension Phase.

Table 8 Schedule of Procedures/Assessments in Study H3B-6545-G000-102

Period	**Screening**	**Cycle 1**					**Cycle 2**			**Cycle 3+**	**EOT**	**Safety Follow-up 28 days (+7 days)**	**Survival[a] Follow-up**
Day	**D-21 to D1**	**D1[b]**	**D8**	**D15**	**D21**	**D28±1[cv]**	**D1**	**D8**	**D15**	**D1**			
Procedure													
Informed consent	X												
Eligibility criteria	X												
Medical history	X												
Concomitant medication/ adverse events	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[d]	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X					X			X	X	X	
Triplicate 12-lead ECG[e]	X	X	X	X	X	X	X			X	X	X	
ECHO or MUGA scan[f]	X									X			
Pregnancy test[g]	X						X			X	X		
Laboratory													
CBC[h]	X	X	X	X	X	X	X	X	X	X	X	X	
CMP[i]	X	X		X			X		X	X	X	X	
Other[j]	X	X		X			X		X	X	X	X	
INR/PT/aPTT[k]	X						X			X	X	X	

Table 8 Schedule of Procedures/Assessments in Study H3B-6545-G000-102

Period	**Screening**	**Cycle 1**					**Cycle 2**			**Cycle 3+**	**EOT**	**Safety Follow-up 28 days (+7 days)**	**Survival[a] Follow-up**
Day	**D-21 to D1**	**D1[b]**	**D8**	**D15**	**D21**	**D28±1[cv]**	**D1**	**D8**	**D15**	**D1**			
Virology (HCV, HBV)[l]	X												
Urine testing dipstick[m]	X						X			X	X	X	
Study treatments dispensing/return[n]		X					X			X	X		
PK samples[o]			X		X	X					X		
PG whole blood	X												
Biomarkers and exploratory analysis													
Tumor biopsy[p]	X												
cfDNA whole blood[q]	X	X								X	X		
Efficacy													
PET scan or whole body bone scan[r]	X	Every 24 weeks in conjunction with the scheduled tumor assessment visit or as clinically indicated											
CT/MRI scans[s]	X	Every 8 weeks until radiological disease progression and as clinically indicated									**X**		
Brain scan[t]	X	As clinically indicated and to confirm CR									X		
Survival follow-up[u]													X

aPTT = activated partial thromboplastin time; CBC = complete blood cell (count); cfDNA = circulating free deoxyribonucleic acid; CMP = comprehensive metabolic profile; CR = complete response; CRF = case report form; CRP = C-reactive protein; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission

tomography; PK = pharmacokinetics; PT = prothrombin time; QTcF = QT interval corrected for heart rate using Fridericia's formula; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

a. All subjects will be followed for survival approximately every 3 months for up to 6 months after the last subject receives their first dose of study treatment. Subjects will be followed for adverse events for 28 days after the last treatment administration. Subjects who discontinue 1 of the 2 drugs and continue therapy with the other one are considered *on treatment* until they discontinue the 2nd drug.

b. With the exception of triplicate 12-lead ECG and cfDNA, other assessments performed during the 7 days prior to Cycle 1 Day 1 should need not be repeated, unless otherwise indicated. On Cycle 1 Day 1, scheduled ECG, vital signs, and laboratory tests should be performed predose.

c. Cycle 2 Day 1 laboratory values for CBC/CMP, INR/PT/aPTT, and urine testing dipstick, can be drawn on Cycle 1 Day 28, in conjunction with the PK blood draw.

d. Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature). Height will be recorded at the baseline visit only.

e. A standard 12-lead ECG will be performed after the patient has been resting for 10 minutes prior to each timepoint indicated. The ECGs should be taken while the patient in a semi-recumbent position. At Screening, triplicate ECGs should be taken approximately 5 minutes apart. On Cycle 1 Day 1, triplicated ECGs should be performed predose. The combined QTcF values will be averaged to provide a single baseline value for each patient. This averaged value will be documented in the ECG section of the CRF. ECG measurements on Cycle 1 Day 8, Cycle 1 Day 21, and Cycle 1 Day 28 should match the PK collection. Triplicate ECGs are to be performed at all visits indicated and should be collected predose on C3D1 and D1 of all subsequent cycles. C1D28 24 hour ECG can also meet the requirement for C2D1 ECG.

f. At screening, at Cycle 3 Day 1, and if clinically indicated thereafter.

g. Pregnancy test during the screening period should be serum (no need to repeat on Cycle 1 Day 1 if within 72 hours). During the study, urine testing should be performed at Day 1 of each cycle or serum testing should be performed to confirm a positive urine testing.

h. CBC count consisting of hematocrit, hemoglobin, total WBC with 5-part differential, and platelet count plus RBC count.

i. CMP panel includes the following: fasting glucose, calcium, albumin, total protein, electrolytes (sodium, potassium, carbon dioxide, and chloride), renal function tests (blood urea/blood urea nitrogen, and creatinine), and liver function tests (ALP, ALT, AST, and bilirubin).

j. Other includes the following: albumin, CRP, fasting lipase, fasting amylase, lactate dehydrogenase, magnesium, phosphorus, gamma-glutamyl transpeptidase, and thyroid function tests (TSH and free T_4).

k. INR, PT, aPTT will be assessed by standard methods at a local laboratory.

l. See Appendix 3 for HBV/HCV testing criteria.

m. If abnormalities are present, microscopic testing should be done.

n. H3B-6545: daily starting Cycle 1 Day 9; palbociclib: daily from Day 1 to Day 21 every 28-day cycle.

o. Plasma samples for PK:

a. *During the escalation part of the study*: On **Cycle 1 Day 8**, PK (palbociclib) blood samples to determine plasma concentrations of palbociclib will be collected at predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days. On **Cycle 1 Day 21**, PK (palbociclib and H3B-

6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose. On **Cycle 1 Day 28**, PK (H3B-6545) blood samples to determine plasma concentrations of H3B-6545 will be collected at predose and 1, 2, 4, 6, 8, and 24 hours postdose.

b. *During the expansion phase*: On **Cycle 1 Day 21**, PK (palbociclib and H3B-6545) blood samples to determine plasma concentrations of palbociclib and H3B-6545 will be collected predose (within 1 hour before administration of study drug) and 1 (±10 minutes), 2 (±15 minutes), 4 (±20 minutes), 6 (±30 minutes), 8 (±30 minutes), and 24 hours (±60 minutes, must be before administration of the next day's dose of study drugs) postdose. These windows apply to PK sampling on other days.

c. *During both phases of the trial*: additional PK blood samples will be collected in conjunction with tumor assessments until EOT or until data cutoff date for the primary analysis, whichever is earlier.

d. Samples should be collected via peripheral vein when possible.

p. New biopsy (preferred) or archival tumor block or slides (15 slides minimum from a surgical specimen, 20 slides minimum from a biopsy) must be provided. If archival tumor tissue is provided, the tumor sample must have been collected after the most recent progression or recurrence. Not required for subjects with bone only disease

q. Whole blood for cfDNA (8 mL) will be collected during the screening period, Cycle 1 Day 1, Cycle 1 Day 21, Cycle 3 Day 1, every 8 weeks thereafter (in conjunction with tumor assessments), and EOT, or until data cutoff date for the primary analysis, whichever is earlier. Two tubes (2×8 mL) will be collected at Screening and EOT.

r. A bone scan using whole-body bone MRI, ^{99}m-technetium-based bone scans, or ^{18}F-sodium fluoride positron emission tomography will be performed during Screening to establish a baseline (a historical bone scan performed within 6 weeks before Cycle 1 Day 1 is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

s. Tumor assessments (CT chest with IV contrast, and CT [oral and IV contrast] or MRI [IV contrast] of the abdomen, pelvis, and other known or suspected sites of disease) will be performed during Screening (Day -21 to Cycle 1 Day 1) and every 8 weeks (±7 days) starting from Cycle 1 Day 1 (ie, 8, 16, 24 weeks) or as indicated if disease progression is suspected clinically. If imaging with contrast, as requested in above, is contraindicated, imaging without contrast should be performed and reason for contraindication should be captured in the source documents.

t. A brain scan (CT with contrast or MRI [pre- and postgadolinium]) will be performed at Screening and as clinically indicated to assess potential for central nervous system disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment timepoints, including EOT. For all subjects, a follow-up brain scan must be performed to confirm CR within 1 week following response confirmation or if clinically indicated.

u. Following progression, all subjects will be followed for survival every 3 months for up to 6 months after the last subject receives their first dose of study treatment. The follow-up can be done by telephone call at the investigator's discretion.

v. Any protocol assessment, including labs, performed within 3 days prior to D1 of the next cycle do not need to be repeated on D1 of the new cycle.

Table 9 Extension Phase

Extension Phase will begin for subjects still on treatment at the time of the data cut-off for primary analysis

Procedure	Treatment[a]	EoT[n]	Safety Follow-Up
Vital signs and weight[b]	X		
Physical examination[c]	X	X	
ECOG performance status	X	X	
12-Lead ECG[d]	X	X	
Echocardiogram or MUGA scan[e]	As clinically indicated	As clinically indicated	
Hematology and clinical chemistry (local lab)[f]	X	X	
Urine dipstick testing[g]	X	X	
Pregnancy test[h]	X	X	
Tumor assessments (CT/MRI)[i]	As per local standard of care but not less frequently than every 12 weeks or earlier if clinically indicated		
Bone Scan[j]	As clinically indicated		
Brain scan (CT/MRI)[k]	As clinically indicated		
Study Treatment	28 Day cycle		
Concomitant medications[l]	X	X	X
AEs/SAEs[m]	X	X	X

AE = adverse event; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HR = heart rate; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; RR = respiratory rate

a. Efforts should be made to conduct study visits on the day scheduled (Cycle X Day 1 ±3 days). The study visit (and safety assessments) still needs to occur regardless of a study medication hold per the visit schedule.

b. Assessments will include vital signs (resting BP [including date and time of measurement], HR, RR, and body temperature) and weight.

c. A symptom-directed physical examination during the study, as clinically indicated.

d. Single 12-lead ECG. Subjects are suggested to be in the recumbent position for a period of 5 minutes prior to obtaining ECG.

e. An echocardiogram or MUGA scan to assess LVEF will be performed as clinically indicated

f. Clinical laboratory assessments will be conducted at a local laboratory. Clinical chemistry and hematology results should be reviewed prior to administration of study drug for all cycles. Assessments may be performed within 72 hours prior to the visit.

g. Urine dipstick testing for subjects should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site).

h. A serum or urine pregnancy test will be performed at Day 1 of every cycle, and at the Off-Treatment assessment in women of childbearing potential (ie, premenopausal and perimenopausal women who have been amenorrheic for less than 12 months).

i. After the data cutoff for the primary analysis: Tumor assessments using contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis and other areas of known disease at screening or newly suspected disease should be performed as per local standard of care but not less frequently than every 12 weeks or earlier if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques that were used for the assessment during the Study Treatment Phase should be used after the data cutoff for the primary analysis.

j. A bone scan to assess bone metastases should be performed as clinically indicated.

k. Brain scans should be performed as clinically indicated.

l. Concomitant medications will be recorded until 28 days after last dose

m. Subjects must be followed for AEs for 28 calendar days after the last dose and complete a safety follow-up visit on the 28th day (with up to + 7 day window).

n. Tumor assessments will only be done in subjects who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

9.6.2.2 Description of Procedures/Assessments Schedule

The description of procedures and schedule of assessments is described in the Schedule of Procedures/Assessments (Table 8).

9.6.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of advanced or metastatic ER+ HER2– breast cancer.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.6.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated With Special Situations

9.6.4.1 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.6.4.2). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

1. Elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN or if elevated greater than the ULN at baseline, then 3× the baseline for the subject

AND

2. Elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN or if elevated greater than the ULN at baseline, then 1.5× the baseline for the subject

AND AT THE SAME TIME

3. Alkaline phosphatase laboratory value that is less than 2× the ULN

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

9.6.4.2 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit. SAEs will be collected for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor or designee to be filed in the sponsor's Trial Master File.

9.6.4.3 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE

and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.6.4.2]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.6.4.4 Reporting of Events Associated With Special Situations

9.6.4.4.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

Symptomatic and nonsymptomatic overdose must be reported in the eCRF system. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 9.6.4.2) if the overdose is symptomatic.

For information on how to manage an overdose of H3B-6545, reach out to the sponsor or CRO; and for palbociclib, refer to the latest palbociclib package insert (Ibrance USPI, 2019).

9.6.4.5 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.6.4.6 Breaking the Blind

Not applicable

9.6.4.7 Regulatory Reporting of Adverse Events

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

For this study, the Reference Safety Information for palbociclib, which the sponsor will use to assess expectedness, is the approved palbociclib (Ibrance) EMA SmPC. All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.6.5 Completion/Discontinuation of Subjects

The investigator may discontinue study drug for a subject at any time for safety or administrative reasons. A subject may elect to discontinue trial therapy or withdraw consent for further participation in the study at any time for any reason. All subjects who withdraw consent for further participation in the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 8).

Subjects will be discontinued from study treatment for any of the following reasons:

- Disease progression*
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (at the investigator's discretion)
- Inability of the subject to comply with study requirements, or subject is lost to follow-up
- Subject requests to discontinue treatment
- Subject withdraws consent from the study
- Pregnancy

**Subjects may continue to receive treatment after progression only if, after discussion with the medical monitor, it is determined that the subject continues to derive clinical benefit.*

After discontinuation from protocol treatment, subjects must be followed for AEs for 28 days after their last dose of study drug. All new AEs, including SAEs, occurring during this period must be reported and all SAEs must be followed until resolution, unless, in the opinion of the investigator, these events are not likely to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for this decision in the

subject's medical records and indicate on the AE pages that the outcome is not resolved on the electronic case report form (eCRF).

All subjects who have Grade 3 or 4 laboratory abnormalities (per NCI CTCAE v5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1, 2, or baseline for the subject, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the subject's medical records and indicate on the AE pages that the outcome is not resolved on the eCRF.

9.6.6 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.7 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

The investigator will permit study-related quality audits and inspections by the sponsor or its representative(s), government regulatory authorities, and the IRB/IEC of all study-related documents (eg, source documents, regulatory documents, data collection instruments, CRFs). The investigator will ensure the capability for review of applicable study-related facilities. The investigator will ensure that the auditor or inspector or any other compliance or quality assurance reviewer is given access to all study-related documents and study-related facilities.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB/IEC, and the sponsor or its representative(s).

9.7.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA

1572 or Investigator and Site Information Form must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.7.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.8 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released and a snapshot of the database is obtained and released). Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.8.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.8.1.1 Study Endpoints

9.8.1.1.1 PRIMARY ENDPOINT

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

9.8.1.1.2 SECONDARY ENDPOINTS

- AEs and SAEs as well as changes in clinical laboratory values, vital sign measurements and ECG parameters
- Standard primary PK parameters, including, but not limited to, the area under the plasma concentration-time curve from timepoint 0 through the last measurable point (AUC_{0-t}), C_{max}, T_{max}, C_{24}, and ratio of the DDI effect
- ORR, defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response (PR+CR)
- DoR, defined as the time from the date of the 1st documented CR/PR until the 1st documentation of disease progression or death, whichever comes first
- CBR, defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response, or durable stable disease (duration is at least 23 weeks)

- PFS, defined as the time from the 1st dose date to the date of the 1st documentation of disease progression or death (whichever occurs 1st)
- OS, defined as the time from 1st dose date to the date of death from any cause.

9.8.1.2 Definitions of Analysis Sets

- *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.
- *Full Analysis Set*: which will consist of all subjects who receive at least 1 dose of study drug.
- *Dose Evaluable Set*: which will consist of all subjects who were evaluable for DLT in Phase 1b. This will be the analysis set for DLT results.
- *Response-Evaluable Set*: 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 postbaseline tumor assessment. This will be the primary analysis set for efficacy evaluations.
- *Pharmacokinetic Analysis Set*: which will consist of subjects who received at least 1 dose of study drug and all valid plasma concentrations (at least 3 valid concentrations for noncompartmental analysis).

9.8.1.3 Subject Disposition

The number of subjects screened for participation and number enrolled overall and by study part will be tabulated along with the proportion included in each analysis population. The proportion of subjects who discontinue the study will be tabulated, along with the primary reason for discontinuation.

9.8.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized descriptively. Data to be tabulated will include at least demographic features such as sex, age, and race, as well as weight and disease-specific status and medical history.

9.8.1.5 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).

The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Full Analysis Set by study part, cohort and overall Anatomical Therapeutic Chemical class (ie, anatomical class, therapeutic class, pharmacologic class, chemical class), as well as WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started after the date of the first dose of study drug up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

9.8.1.6 Efficacy Analyses

All efficacy parameters will be summarized descriptively for the Response-Evaluable Set and Full Analysis Set.

9.8.1.6.1 PRIMARY EFFICACY ANALYSIS

Not applicable.

9.8.1.6.2 SECONDARY EFFICACY ANALYSES

ORR and CBR will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson.

DoR will be calculated for subjects achieving a best overall response of confirmed PR+CR.

For DoR, PFS, and OS, medians will be calculated using Kaplan-Meier estimates. DoR, PFS, and OS will be reported in both summary tables and plotted with Kaplan-Meier curve.

9.8.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.8.1.7.1 PHARMACOKINETIC ANALYSES

The plasma concentrations of palbociclib and H3B-6545 will be presented by dose level and day, as the number of subjects with data, geometric mean, mean, standard deviation (SD), median, minimum, and maximum values by nominal sampling timepoint. The PK parameters will include, as applicable, C_{max} (maximum observed plasma concentration), T_{max} (time of the maximum observed plasma concentration), $AUC_{0\text{-}24}$ (AUC from zero time to 24 hours), $AUC_{0\text{-}t}$ (AUC from zero time to last measurable concentration), $AUC_{0\text{-}inf}$ (AUC from zero time to infinity), percentage of AUC that is due to extrapolation from the last measurable concentration to infinity ($\%AUC_{Extrap}$), apparent terminal disposition rate constant (λ_z), apparent plasma terminal elimination half-life, apparent total plasma clearance (CL/F), and apparent volume of distribution (V/F) and will be summarized by cohorts and day, with the number of measurements, number of non-missing data, the number of subjects, geometric mean (CV%), mean, SD, median, minimum, and maximum.

The DDI effect will be estimated as a ratio of exposure index (C_{max}, $AUC_{0\text{-}24}$, and C_{24}) in the following way in the dose escalation cohort: ratio of palbociclib exposure on Day 21/palbociclib exposure on Day 8 for potential effect of H3B-6545 on palbociclib and ratio of H3B-6545 exposure on Day 21/H3B-6545 exposure on Day 28 for potential effect of palbociclib on H3B-6545. This ratio will be summarized by cohorts with the number of subjects, geometric mean (CV%), mean, SD, median, minimum, and maximum.

9.8.1.7.2 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, PR, 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 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 will be reported separately.

9.8.1.8 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 using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and 12-lead ECG results.

Safety will be assessed through the analysis of the reported incidence of TEAEs. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized using system organ class (SOC) and preferred term (PT). In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE v5.0 grade, and AEs related to study treatment will also be presented by dose level.

Other safety endpoints, including laboratory results, vital signs, and ECG findings, will be summarized for all subjects in the Safety Analysis Set.

9.8.1.8.1 Extent of Exposure

Descriptive statistics for subjects treated, including the duration of treatment, and the number of subjects requiring dose changes, will be presented. A by-subject listing of the date of study drug administration and the dose administered will be presented. Details will be provided in the SAP.

9.8.1.8.2 Adverse Events

The AEs will be coded using MedDRA and summarized using SOC and PT. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE v5.0 grade, and AEs related to study treatment will also be presented by dose level.

AEs will be collected for each subject until 28 days after last trial therapy administration.

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. 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 SOC are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized. 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.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum CTCAE grade.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

In the Dose-Evaluable Set, the number (percentage) of subjects with DLTs will be presented by dose level for Phase 1b of the study. A listing of subjects with DLTs will be provided.

9.8.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.6.1.4.3, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using descriptive statistics. Qualitative parameters listed in Section 9.6.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Furthermore, the frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be tabulated for selected laboratory parameters to include at least, hemoglobin, WBC, ANC, lymphocytes, platelet count, alkaline phosphatase, AST, ALT, bilirubin, creatinine, and electrolytes. Shift tables will also be produced for these parameters based on the baseline CTCAE grade and the maximum CTCAE grade post baseline. Details will be provided in the SAP.

9.8.1.8.4 VITAL SIGNS

Changes in vital sign parameters (including systolic and diastolic BP, heart rate, respiratory rate, and temperature) and body weight will be summarized over time, and any abnormal values will be tabulated.

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, and weight) and changes from baseline will be presented by visit.

9.8.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed throughout the study according to the schedule of assessments. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

Summary tables and listings for the various intervals (eg, QT and pulse rate) and changes from baseline will be presented. Additional analysis will be detailed in the SAP.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

- Absolute QTcF interval prolongation:
  QTcF interval >480 ms

  QTcF interval >500 ms

- Change from baseline in QTcF interval:

QTcF interval increases from baseline >30 ms

QTcF interval increases from baseline >60 ms

QTcF interval >500 ms and QTcF interval increases from baseline >60 ms

All ECG abnormalities will be listed on a per-subject basis.

9.8.2 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.

9.8.3 Interim Analysis

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.

9.8.4 Other Statistical/Analytical Issues

Not applicable.

9.8.5 Procedure for Revising the Statistical Analysis Plan

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.

10 REFERENCE LIST

Ahn C. An evaluation of Phase 1 cancer clinical trial designs. Stat Med. 1998;17(14):1537–49.

Dillman RO, Koziol JA. Phase 1 cancer trials: limitations and implications. Mol Biother. 1992;4(3):117–21.

Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925–36.

Gatsonis C, Greenhouse JB. Bayesian methods for Phase 1 clinical trials. Stat Med. 1992;11(10):1377–89.

Hamilton EP, Dees EC, Judy Wang SZ, Kim A, Korpal M, Rimkunas V, et al. Phase I dose escalation of H3B-6545, a first-in-class highly Selective ERα Covalent Antagonist (SERCA), in women with ER-positive, HER2-negative breast cancer (HR+ BC). J Clin Oncol. 2019;37(15 Suppl):1059. Epub 20 May 2019.

Hortobagyi GN, Stemmer SM, Burris HA, Elmeliegy M, Germa C, O'Shaughnessy J, et al. Updated results from MONALEESA-2, a Phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor–positive, HER2-negative advanced breast cancer. Ann Oncol. 2018;29(7):1541–7.

Ibrance® EMA Summary of Product Characteristics (SmPC) by Pfizer Limited Available from: https://www.medicines.org.uk/emc/product/4449/smpc. Last updated on emc on 20 Feb 2020.

Ibrance® United States Prescribing Information, Revised 9/2019. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=2191. Accessed 07 Nov 2019.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. General Considerations for Clinical Trials, E8 1997. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf.

National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [27 Nov 2017]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

Smith PG, Puyang X, Furman C, Zheng GZ, Banka D, Thomas M, et al. Discovery and development of H3B-6545: a novel, oral, Selective Estrogen Receptor Covalent Antagonist (SERCA) for the treatment of breast cancer. Cancer Res 2017;77(13 Suppl): Abstract DDT01–04. doi: 10.1158/1538-7445.AM2017-DDT01-04.

Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2018;379:1926–36.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor *(or appropriate study team member)* and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as an Interactive Voice/Web Response System (IxRS), x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Reasons for discontinuation of study treatment,
- comments and other information on AEs [eg, severity, relationship to study drug, outcome],

- reasons for dose modification, indication for prior/concomitant medication,
- sampling times for drug concentrations,
- sampling times for clinical laboratory tests.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 for US sites), Investigator and Site Information Form (for non-US sites), ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 15 years following the completion of the study.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the PI (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA *(or designated contractor)* or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Concomitant Medications

Combination administration of study drugs could result in DDIs that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or H3B-6545.

Use of antacids is allowed.

The use of palonosetron, prochlorperazine, promethazine, and cyclizine for management of nausea and vomiting is also allowed. The use of ondansetron and granisetron is not permitted because of their potential to prolong QT interval.

Herbal preparations/medications are not allowed throughout the study; thus, the subject should stop using herbal medications 7 days prior to the first dose of H3B-6545. These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng.

The list of prohibited medications is based on FDA guidance (October 2017, https://www.fda.gov/media/82734/download) and its table of substrates, inhibitors and inducers (updated as of 12/03/2019, https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

Appendix 2 ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed <50% of the time Ambulatory and capable of all self-care but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed >50% of the time Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Appendix 3 HBV/HCV Testing Criteria

Eligibility Based on Serologic Markers for Hepatitis B and Hepatitis C

Test	Result				
HBsAg	+	-	-	-	-
HBcAb	Any	+	-	+	-
HBsAb	Any	-	+	+	-
HCV Ab	Any	Any	-	-	-
Eligibility	Not Eligible	Not Eligible	Eligible	Eligible	Eligible

If indeterminate results are obtained, viral DNA (hepatitis B) or RNA (hepatitis C) should be measured to confirm negative viral status.

HCV Ab positive: Indicates active infection and risk for reactivation. These patients are not eligible for this trial.

HBsAg positive: Indicates active infection and risk for reactivation with fulminant hepatitis. These patients are not eligible for this trial.

HBcAb positive and HBsAb negative: indicate active infection and risk for reactivation. These patients are not eligible for this trial.

HBsAb positive: As a standalone marker, it indicates successful vaccination or previous infection that has been successfully resolved if it is the only positive finding. These patients are eligible for this trial.

HBsAg negative, HBcAb positive, HBsAb positive: Resolved or latent infection. These patients are eligible for this trial.

All markers negative: No prior exposure or vaccination to hepatitis B and no prior exposure to Hepatitis C. Patients are eligible for this trial

PROTOCOL SIGNATURE PAGE

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
Investigational Product Name:	H3B-6545 and palbociclib
IND Number:	133282
EudraCT Number:	2019-004622-17

SIGNATURES

PPD

Sep 2022

Date

PPD

Eisai, Inc.

PPD

Sep 2022

Date

PPD

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

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
Investigational Product Name:	H3B-6545 and palbociclib
IND Number:	133282
EudraCT Number:	2019-004622-17

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>		
Investigator	Signature	Date

As regionally required.

<Name, degree(s)>		