Study information

Title	Prospective, multicenter, observational study to evaluate patient-reported outcome and physical activity using smartphone-based application and wearable device in Japanese patients with HR+/HER2- advanced breast cancer treated with palbociclib plus endocrine therapy or endocrine monotherapy
Study Phase	Not applicable
Protocol number	A5481126
Protocol version identifier	Amendment 3
Date	20 December 2021
Active substance	Palbociclib (L01XE33)
Medicinal product	Palbociclib (IBRANCE)
Research question and objectives	The primary objectives of this prospective observational study are to assess change in EORTC-QLQ-C30 and physical activity in Japanese patients with HR+/HER2- advanced breast cancer receiving: 1) Palbociclib plus endocrine therapy (Group 1) or 2) Endocrine monotherapy (Group 2)
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first line
2L	second line
ABC	advanced breast cancer
AE	adverse event
BC	breast cancer
BYOD	Bring Your Own Device
CDK4/6	cyclin-dependent kinases 4 and 6
CI	confidence interval
CRF	case report form
CSA	clinical study agreement
CT	Clinical Trial
DCT	data collection tool
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDP	exposure during pregnancy
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–30 (items)
ePRO	electronic PRO
ER	estrogen receptor
ER+	estrogen receptor positive
FACT-B	Functional Assessment of Cancer Therapy – Breast Cancer
HER2-	human epidermal growth factor 2 - negative
HR	hormone receptor
HR+	hormone receptor - positive
HRQOL	health-related quality of life
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
iOS	operating system
IRB	Institutional Review Board
JBCRG	Japan Breast Cancer Research Group
JFCR	Japanese Foundation for Cancer Research
J-RMP	Japan Risk Management Plan
MHLW	Ministry of Health, Labour and Welfare
MVPA	moderate to vigorous physical activity
PFS	progression-free survival
PRO	patient reported outcome
PRO-CTCAE	Patient Reported Outcome - Common Terminology Criteria for Adverse Events

QOL	quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
SRSD	single-reference safety document
TTD	time to deterioration
TTF	time to treatment failure
US-NCI	United States - National Cancer Institute

2. RESPONSIBLE PARTIES

This study will be conducted as a Pfizer-sponsored, prospective, multicenter, observational study, in support of Japan Breast Cancer Research Group (JBCRG), outsourced by Pfizer.

Pfizer prepares original draft of study concept and protocol and receives scientific advices from Principal Investigator and the Executive Committee members assigned by JBCRG. In addition, the protocol will be reviewed by the JBCRG Clinical Trial Review Committee and JBCRG governance board in terms of academic significance, feasibility, and validity of the study design.

Executive committee members in this study provide advice on the protocol synopsis, protocol, study conduct, and handling of operational issues from the medical and scientific perspectives; provide advice on site selection and data review during the study; and conduct interpretation of the data obtained in this study (including abstract and manuscript) and publication of the study data as co-authors.

Executive committee consists of JBCRG and Pfizer, and this study will be operated by JBCRG and Pfizer. Site selection will be covered by JBCRG, and data management and monitoring will be covered by Pfizer or a third party vendor designated by Pfizer. Data analysis will be covered by a JBCRG and independent third party vendors designated by Pfizer.

2.1. Responsible parties in JBCRG

Research Organization

Representative PPD of JBCRG;
PPD (Department of Breast and Endocrine Surgery, Graduate school of Medicine, Nagoya University,)

Executive Committee members in this study

Name, degree(s)	Affiliation
PPD MD (Principal Investigator)	Department of Breast and Endocrine Surgery, University of Tsukuba Hospital
PPD MD	Department of Medical Oncology, Fukushima Medical University
PPD MD	Department of Breast and Endocrine Surgery, Tokai University School of Medicine
PPD	Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry

PPD MSc.	Department of Clinical Trial Data Management, Tokyo University Graduate School of Medicine

Investigators and Investigational sites

See Appendix 1.

2.2. Responsible parties in Pfizer

Protocol author

Name, degree(s)	Affiliation
PPD (Low-Interventional Study Lead)	Breast cancer team, Medical Affairs, Oncology, Pfizer Japan

Data center, Monitoring facility and audit facility

See Appendix 1.

3. SUMMARY

Not applicable.

4. AMENDMENTS AND UPDATES

Document History

Document	Version Date	Rationale
Original protocol	1 June 2020	Not applicable (N/A)
Amendment 1	1 September 2020	To clarify the role and responsibility for each organization in this study, descriptions in Section 2 and related sections were modified. As PRO data collection for "palbociclib use" was removed, descriptions in Section 6 and related sections were modified. Other minor edits were made.
Amendment 2	01 October 2021	To update and change the research organization and responsible parties, description in Section 2 was revised. To clarify that the target population in this study is a patient who initiates first or second line endocrine-based treatment, descriptions in Section 8.1, Figure 1 and 9.1.1 were revised. Following the revised Japanese Breast Cancer Society Clinical Practice Guideline, the number of patients who initiate endocrine monotherapy in the first or second-line setting has decreased thus it has become difficult to accumulate patients in Group 2, and the number of patients in Section 9.1 has been revised accordingly. Based on the comments from Independent Ethics Committee, descriptions were added in Section 15.1 and Section 19.1.
Amendment 3	20 December 2021	To update the planned dates of milestone based on actual enrollment speed, description in Section 5 and Section 9.1 were revised.

5. MILESTONES

Milestone	Planned date
Start of data collection	01 February 2021
End of patient enrollment	31 August 2022
End of data collection	28 February 2023
Final study report	31 December 2023

6. SCHEDULE OF ACTIVITIES

Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Procedure / Assessment	Screening	Baseline	Observation period (6 cycles; 24 weeks)[j]		End of Study[c]
			Weekly[a]	Cycle-base[b]	
Time Window			**+ 3 days[d]**	**+ 7 days[d]**	
Informed consent	X				
CRF data					
Patient baseline characteristics; Demography, Height, Weight, Medical history, Prior treatment and surgery history, Primary diagnosis, Site of metastatic and disease, Menopausal status, Treatment being initiated, Line of therapy		X			
ECOG performance status[k]		X	←X→		X
Adverse event monitoring (eg, type, grade)[e]	←X→				
Treatment (eg, type, duration)[f]			←X→		
Palbociclib dosing modification[g]			←X→		
Concomitant Medication (Surgery, Radiotherapy)			←X→		
Disease progression (if applicable)			←X→		
Initial treatment discontinuation (if applicable)			←X→		
Study withdrawal (if applicable)			←X→		
Study completion					X
PRO data via smartphone-based application					
Patient baseline characteristics; Education, Employment		X[i]			
EORTC-QLQ-C30		X[i]		X	
PRO-CTCAE[h]		X[i]	X		
Overall satisfaction with treatment				X	

Procedure / Assessment	Screening	Baseline	Observation period (6 cycles; 24 weeks)[j]		End of Study[c]
			Weekly[a]	Cycle-base[b]	
Time Window			**+ 3 days[d]**	**+ 7 days[d]**	
Physical activity data via wearable device					
Physical activity		X	←X→		

a. Weekly assessment of PRO-CTCAE will be conducted based on Cycle 1 Day 1 regardless of cycle delay.
b. Cycle-based assessment of EORTC-QLQ-C30 and Treatment satisfaction will be conducted on Day 15 of each cycle.
c. End of study is defined as end of 6 cycles of initiated treatment. If patients discontinue the initiated treatment before completion of 6 cycles (eg, due to disease progression) and switch to another treatment, end of study will be end of 24 weeks after initiation of initial treatment. In this case, to assess association between change in QOL and physical activity versus disease progression, data collection [including PROs (EORTC-QLQ-C30 and PRO-CTCAE) and physical activity evaluation, EDC data entry] will continue to the end of the study (ie, 24 weeks after the start of the study) even if the treatment is switched to another treatment.
d. Weekly-based assessments will remain open for up to 3 days (72 hours) and cycle-based assessments will remain open for up to 7 days (168 hours).
e. Safety reporting will follow applicable regulations and is detailed in Section 16.
f. Type and duration of treatment for advanced breast cancer used during observation period in this study (including endocrine therapy used in combination with palbociclib) will be collected in both group.
g. Group 1 only.
h. "Fatigue" and "General pain" are measured as PRO-CTCAE.
i. Baseline assessment for PRO data will be conducted after obtaining informed consent and before initiating study treatment.
j. The observation period in this study will be 6 cycles. In Group 1 (palbociclib plus endocrine therapy), palbociclib is administered for 3 consecutive weeks followed by 1 week off treatment to comprise 1 cycle of 4 weeks. If palbociclib is temporarily interrupted (eg, due to adverse event) and the start of the next cycle is delayed, the duration of one cycle may exceed 4 weeks, then, the observation period may exceed 24 weeks. In Group 2 (endocrine monotherapy), 1 cycle is defined as 4 weeks.
k. To be assessed at Baseline and End of study. If ECOG performance status is assessed during the observation period, the data will be entered into EDC. If patients discontinue the initiated treatment before completion of 6 cycles (eg, due to disease progression) and switch to another treatment, ECOG performance status will be assessed at end of treatment as well.

7. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer in women in Japan, with nearly 86,500 new cases diagnosed in 2018 and the incidence rate has steadily increased. In 2017, there are 14,800 deaths as breast cancer patients. Breast cancer prevalence rate of Japanese women by age group began to increase from the 30s, peaked in the latter half of the 40s, after that it remained almost constant, and gradually decreased from the late sixties.

Approximately 25% of women who are diagnosed with early-stage breast cancer will develop distant metastases. The most common subtype of advanced breast cancer is hormone receptor-positive, human epidermal growth factor 2-negative advanced breast cancer (HR+/HER2-ABC). For ER-positive breast cancer, it is relatively common to relapse after a long period of time, eg, 10 or more years after diagnosis. After experiencing a distant recurrence, patient prognosis is poor, and the overall 5-year relative survival rate is 27% for distant-stage disease. According to The Japanese Breast Cancer Society Clinical Practice Guidelines for Breast Cancer 2018, the objectives for metastatic/recurrent breast cancer are (1) The prolongation of survival and (2) The improvement/maintenance of the quality of life.

Palbociclib is a selective, oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that prevents cell proliferation by blocking cell cycle progression from the G1 to the S phase. In Japan, palbociclib was approved in 2017 for the treatment of HR+/HER2- inoperable or recurrent breast cancer. The safety and efficacy of palbociclib were investigated in two phase 3, randomized, double-blind, placebo-controlled, multicenter trials (PALOMA-2 and PALOMA-3).

PALOMA-2 demonstrated that median progression-free survival (PFS) was 24.8 months with palbociclib + letrozole and 14.5 months with placebo + letrozole (hazard ratio=0.58 [95% CI, 0.46-0.72] P<0.000001) as initial therapy for postmenopausal women with ER+/HER2- ABC. In Japanese subgroup analysis in PALOMA-2, median PFS was 22.2 months with palbociclib + letrozole vs 13.8 months with placebo + letrozole (hazard ratio=0.59 [95% CI, 0.26-1.34]). Common adverse events (AEs; all grades) with palbociclib + letrozole vs placebo + letrozole were neutropenia (81.8% vs 6.3%), infections (62.6% vs 45.0%), leukopenia (40.3% vs 2.3%), fatigue (39.6% vs 28.4%), arthralgia (37.6% vs 36.9%), nausea (37.2% vs 27.0%), 14.0%), alopecia (33.6% vs 16.2%), stomatitis (31.5% vs 14.9%). Grade 3/4 neutropenia occurred in 69.1% in patients with palbociclib + letrozole. The incidence rate of neutropenia with combination therapy was higher in the Japanese than in the overall population (neutropenia, 93.8% vs 79.5%). Grade 3/4 neutropenia occurred in 87.5% of Japanese patients with palbociclib + letrozole. In PALOMA-2, FACT-B was used to assess patient-reported outcome (PRO). There was no significant difference between palbociclib + letrozole and placebo + letrozole in overall change from baseline in FACT-B scores, despite the longer duration of treatment in the combination arm, and no significant difference in FACT-B HRQOL based on FACT-B total scores. The analysis of time to deterioration (TTD) in FACT-B showed a positive trend (hazard ratio<1) favoring the palbocilib + letrozole arm but

was not statistically significant (hazard ratio=0.883 [95% CI, 0.673-1.158]; one-sided *P*=0.19).

Another phase 3 study, PALOMA-3, was conducted with HR+/HER2- patients that had relapsed or progressed during prior endocrine therapy. The median PFS was 9.2 months with palbociclib + fulvestrant and 3.8 months with placebo + fulvestrant (hazard ratio=0.42 [95% CI, 0.32-0.56] *P*<0.001). In Japanese subgroup analysis in PALOMA-3, median PFS was 13.6 months in palbociclib + fulvestrant and 11.2 months in placebo + fulvestrant group (hazard ratio= 0.82 [95% CI, 0.32-2.11]). Common AEs with palbociclib + fulvestrant vs placebo + fulvestrant were neutropenia (84.1% vs 3.5%), leukopenia (60.0% vs 5.2%), infections (54.5% vs 34.9%), fatigue (44.1% vs 31.4%), Nausea (35.9% vs 30.8%), Anemia (31.6% vs 14.0%), Stomatitis (30.1% vs 14.0%). Grade 3/4 neutropenia occurred in 69.6% of patients. Among Japanese patients, neutropenia was most common AE in the palbocilib arm (93%) and typically grade 3/4. Accordingly, dose reduction, cycle delays, and dose interruptions were higher in Japanese patients than in the overall populations. In PALOMA-3, EORTC-QLQ-C30 and EORTC-QLQ-BR23 were used to asses PRO. Analysis of PROs between the two treatment groups showed that estimated overall global QOL scores in EORTC-QLQ-C30 significantly favored the palbociclib + fulvestrant (66.1, [95% CI, 64.5-67.7] versus 63.0 [95% CI, 60.6-65.3]; *P*=0.0313). Significantly greater improvement from baseline in pain was also observed in this group (-3.3 [95% CI, -5.1 to -1.5] versus 2.0, [95% CI -0.6 to 4.6]; p=0.0011]). Also, TTD in global QOL and pain were significantly delayed (hazard ratio=0.64 [95% CI, 0.45-0.91; *p*<0.007, hazard ratio=0.64 [95% CI, 0.49-0.85; *p*<0.001, respectively]).

Cancer treatment is taking place in an outpatient setting. The growing number of oral and subcutaneous medications for oncological diseases lead to new challenges for patients and health care providers. Some of the challenges include continuous patient-physician communication, lack of adherence, potential side effects, which are common and often underreported, and their impact on quality of life (QOL). One of the important purposes of treatment for ABC patients is to improve or maintain QOL, thus, appropriate assessment of patients' QOL and the effect to daily life are important and desirable to making appropriate treatment decisions and assisting in timely delivery of care.

ePRO technologies can provide a new opportunity for routine monitoring to assess patients' condition, because the ability to assess PROs in real-time enables quick clinical decision-making and intervention. In addition, application of ePRO might enable better patient-clinician communication and lower symptom distress. Also, this kind of ministering provides a systematically collected symptom data and, thus eventually supports clinical decision-making to improve symptom management, which could save a lot of health care provider's time, reduce the number of patients' visits and could enhance adherence.

Wearable devices can objectively measure physical activity. With the rapid development and commercialization in recent years, it has become possible to easily measure patients' physical activity using wearable devices. Gresham et al.,2018 summarized 41 randomized

trials using wearable devices conducted on cancer patients between 2005 and 2016, consistent with the trend in recent years that increasing number of clinical trials have examined the relationship between physical activity and clinical outcomes. Some of these studies have suggested that the physical activity of cancer patients correlates with the patient's performance status, quality of life and survival.

To date, there have been few studies in Japan evaluating the day-to-day effects of ABC treatment on patients in a real-world setting, and information about the effects of treatment-induced AEs on patients' daily functioning outside the context of clinical trials is particularly lacking. This study will provide prospective, observational data in the real-world setting to evaluate the impact of ABC treatment and the treatment-related AEs on patients' daily life utilizing novel technologies (ie, ePRO and wearable device).

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Objectives

Primary objective

Assess change in (1) PRO as measured by EORTC-QLQ-C30 collected via smartphone-based application and (2) physical activity as measured by wearable device in Japanese patients with HR+/HER2- advanced breast cancer receiving below endocrine-based treatment as first or second line setting:

1. Palbociclib plus endocrine therapy (Group 1) or
2. Endocrine monotherapy (Group 2)

NOTE: The study is not intended to compare outcomes between the two groups as primary objective.

Secondary objectives

The following research objectives will be addressed separately for both Group 1 and 2.

- Assess the association between change in EORTC-QLQ-C30 and physical activity versus investigator-reported adverse event (AE)
- Assess the association between change in EORTC-QLQ-C30 and physical activity versus patient-reported symptom as measured by PRO-CTCAE collected via smartphone-based application
- Assess the association between change in EORTC-QLQ-C30 versus change in physical activity

- Assess the association between change in EORTC-QLQ-C30 and physical activity versus disease progression
- Assess the feasibility of collecting physical activity data with wearable device in Japanese patients with advanced breast cancer
- Assess patient's treatment satisfaction (collected as single item via smartphone-based application)
- Evaluate concordance and discordance between investigator-assessed AE versus PRO-CTCAE
- Characterize patients with HR+/HER2- ABC initiating each group treatment (eg, baseline patient demographics and clinical characteristics)

The following research objectives will be addressed Group 1 only.

- Describe dosing patterns (eg, dose reduction, dose interruptions, cycle delay)

CCI [redacted]

[redacted]

- [redacted]
- [redacted]

8.2. Research Endpoints

Primary endpoint

- EORTC-QLQ-C30 (Global health status scale)
- Physical activity metrics (Sedentary time)

Secondary endpoints

- Other EORTC-QLQ-C30 subscales
- Other physical activity metrics (Steps, MVPA time)
- Adverse events and any laboratory abnormalities (Type, incidence, severity, seriousness and relationship to study medications)
- PRO-CTCAE (Fatigue and General pain)

- Disease progression
- Patient treatment satisfaction
- Palbociclib treatment (including dose, dose reduction, dose interruption, cycle delay)

9. RESEARCH METHODS

9.1. Study design

The study is a prospective, multicenter, observational study to evaluate PRO and physical activity using smartphone-based application and wearable device in Japanese patients with HR+/HER2- ABC.

Patients will be enrolled into either palbociclib plus endocrine therapy group (Group 1) or endocrine monotherapy group (Group 2) based on the discretion of the treating physician under routine clinical practice. Total target number of patients is approximately one-hundred in this study (assuming about 20 to 80 patients in each group). The number of enrolled patients will be monitored, and the enrollment will be completed when 100 patients have been enrolled. Of note, the patient who is informed about this study for participation at the time when the number of enrolled patients reaches 100 is allowed to enroll.Enrolled patients will download a smartphone-based application for electronic PRO (ePRO), be provided access to and trained on the use of the application to complete baseline, weekly, and cycle-based assessments for 6 cycles (24 weeks). In addition, enrolled patients will be provided with wearable device and requested to wear the device at all-times, except of while bathing and sleeping, for 6 cycles (24 weeks).

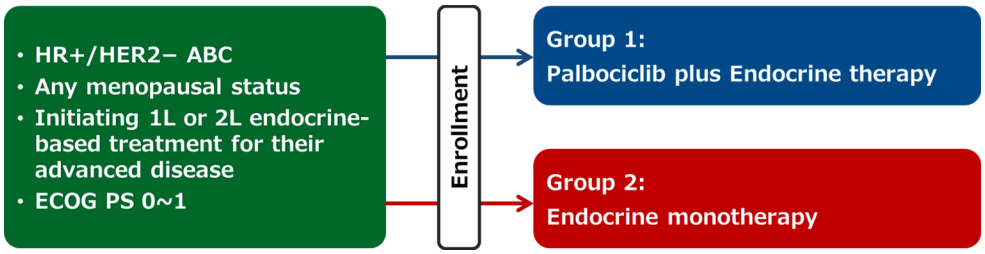
In this study, one cycle is defined as follows;

- In Group 1 (palbociclib plus endocrine therapy), palbociclib is administered for 3 consecutive weeks followed by 1 week off treatment to comprise one cycle of 4 weeks. If palbociclib is temporarily interrupted (eg, due to adverse event) and the start of the next cycle is delayed, the duration of one cycle may exceed 4 weeks, then, the observation period may exceed 24 weeks.
- In Group 2 (endocrine monotherapy), one cycle is defined as 4 weeks.

Participation in this study is not intended to change the routine treatment that patients receive as determined by their prescribing clinicians; all treatment decisions and type and timing of disease monitoring are at the discretion of the treating physician. No additional visits to the clinic will be required for the purposes of the study.

Figure 1 summarizes the overall study design.

Figure 1. Study Design



It is anticipated that all data collection for this study will occur over a 24-month period (from the first patient's first visit to the last patient's end of study assessment),

Planned patient enrollment duration: 18 months

Planned data collection for an individual patient: 6 cycles (24 weeks*)

*In Group 1, if palbociclib is temporarily interrupted (eg, due to adverse event) and the start of the next cycle is delayed, the duration of one cycle may exceed 4 weeks, then, the observation period may exceed 24 weeks.

9.1.1. Inclusion criteria

Patients diagnosed with HR+/HER2- ABC will be enrolled into this study across multiple centers in Japan. All patients will be required to have had a diagnosis of metastatic BC or advanced breast cancer not amenable to resection or radiation therapy with curative intent at the time of study entry.

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Adult women (≥ 20 years of age)
2. Diagnosis of adenocarcinoma of the breast with evidence of metastatic disease or advanced disease not amenable to resection or radiation therapy with curative intent.
3. Documented evidence of HR+/HER2- tumor based on the patient's surgical specimen or most recent tumor biopsy.
4. Initiating first or second line endocrine-based treatment at study entry with one of the following therapies: palbociclib plus endocrine therapy or endocrine monotherapy (eg, letrozole, anastrozole, exemestane, fulvestrant, tamoxifen, toremifen).
5. ECOG performance status = 0~1.
6. Owns or has regular access to an Apple iPhone (iOS 10.0 or later) or Android phone (eg, Nexus or Galaxy with latest software: version 4.4 or greater).

7. Willing and able to complete collection of data via smartphone-based application.

8. Willing and able to wear the wearable device for approximately 6 months.

9. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

10. Able to read and understand Japanese.

9.1.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. The patient is participating in any interventional clinical trial that includes investigational or marketed products. Patients participating in other investigator-initiated research or non-interventional studies can be included as long as their standard of care is not altered by the study.

2. The patient is on active treatment for other malignancies other than ABC.

3. The patient's lifestyle is fluctuating in weekly-basis (eg, shift-time worker), which may have high impact on physical activity assessment based to investigator's discretion.

9.1.3. Variables

Information collected in the data collection materials will be directly transformed into variables; Patient baseline characteristics, treatment (type, duration, treatment modification), patient medical information (eg, adverse event) collected in the EDC system (eCRF); PROs collected in the smartphone-based application (see Schedule of Activity). EORTC-QLQ-C30 and PRO-CTCAE will be scored according to each instrument's scoring algorithm. Physical activity metrics (eg, sedentary time) will be derived by Actigraph's algorithms based on the raw data collected by the device (Actigraph Insight Watch).

Detailed definitions of additional variables that will be derived from the collected data for the statistical analysis will be included in the SAP.

9.1.3.1. Data sources

Data for this study will be obtained via the following sources:

- **Patient medical information:** The investigator or designated study site staff will record clinical and treatment data from patients' medical records into an eCRF promptly at baseline, during the observational period, and at the end of the observational period. Types of data to be obtained from patient medical records are described in Section 6 "Schedule of Activities".

- **Patient-Reported Outcome data:** All patients will be asked to complete a baseline questionnaire, as well as series of questions at weekly, and cycle-based intervals via a smartphone-based application downloaded onto their smartphones. PRO data entered in smartphone-based application will be transferred into the server hosted by the designated PRO vendor. Two validated PRO instruments will be administered at baseline and weekly-basis (PRO-CTCAE) or cycle-basis (EORTC-QLQ-C30). Appropriate agreements with the copyright owners will be in place for use in this study.

- **Physical Activity data:** All patients will be asked to wear a wearable device to record their physical activity. Physical activity raw data will be uploaded from the device to Actigraph CentrePoint cloud during each site visit.

- **Site characteristics information:** Basic site characteristics, including geographic location, will be collected via Pfizer's internal system, if applicable.

10. STUDY PROCEDURES

Screening and Baseline period

Study investigators will screen patients for eligibility, obtain informed consent, and enroll patients meeting the eligibility criteria. Informed consent must be obtained before any study specific procedures are performed. Patient eligibility will be reviewed and confirmed by investigator or study site staff before patients are enrolled in the study.

Investigators or study site staff will complete eCRFs to capture demographic, medical history, and treatment information at screening listed in Section 6 SCHEDULE OF ACTIVITIES.

Enrolled patients will download a smartphone-based application for ePRO into their own device (ie, Bring Your Own Device [BYOD]), be provided access to and trained on the use of the application to complete baseline, weekly, and cycle-based assessments for 6 cycles. As for data to be evaluated, see "PRO data via smartphone-based application" in Section 6 "Schedule of Activities". Patients will complete baseline assessment for EORTC-QLQ-C30 and PRO-CTCAE at study site, if possible.

Investigators or study site staff will assign the wearable device to patients, and patients will be provided with the assigned device and be requested to wear the device at all-times, except of while bathing and sleeping, for 6 cycles. As baseline observation period, it is recommended to wear the device soon after obtaining informed consent until initiating the study treatment. At least 4 days is recommended for baseline observation period to obtain stable baseline data, but treatment schedule of each patient should be prioritized.

Observation Period

The observation period in this study will be 6 cycles (24 weeks).

In Group 1, palbociclib is administered for 3 consecutive weeks followed by 1 week off treatment to comprise 1 cycle of 4 weeks. If palbociclib is temporarily interrupted (eg, due to adverse event) and the start of the next cycle is delayed, the duration of 1 cycle may exceed 4 weeks, then, the observation period may exceed 24 weeks. In Group 2, one cycle is defined as 4 weeks.

Patients will complete PRO assessment in weekly, and cycle-basis and wear the wearable device for 6 cycles. At the patients' regular clinical visits at approximately 30 day interval, they will bring the device worn in the past period, and study site staff will confirm if the returned wearable device is still functional and upload the physical activity data through Actigraph application (ie, ActiSync) into the Actigraph cloud system (ie, Actigraph CentrePoint). Detailed information will be included in User Manual and training for Actigraph CentrePoint for the sites. For the PRO and physical activity data collected from the patient, the data entry status or wearing status will be confirmed, but the data itself will not be confirmed. In addition, investigators or study site staff will complete eCRF to capture treatment changes and clinical outcomes (eg, adverse event) for 6 cycles after enrollment listed in SCHEDULE OF ACTIVITIES.

If a patient has not entered any data through ePRO application for 4 consecutive weeks or if a patient has not worn the wearable device for 4 consecutive weeks, the study site staff will be notified and asked to reach out to the patient.

Even if patients discontinue the initiated treatment before completion of 6 cycles and switch to another treatment, to assess association between change in QoL and physical activity versus disease progression, data collection (including PROs [EORTC-QLQ-C30 and PRO-CTCAE] and physical activity evaluation, EDC data entry) will continue to the end of the study (ie, 24 weeks after initiation of initial treatment).

End of Study

End of study is defined as end of 6 cycles of initiated treatment. If patients discontinue the initiated treatment before completion of 6 cycles (eg, due to disease progression) and switch to another treatment, end of study will be end of 24 weeks after initiation of initial treatment.

Investigators or study site staff will complete CRF to capture End of Study information listed in Section 6 SCHEDULE OF ACTIVITIES.

Patients will return the wearable device to study site staff. Study site staff will stop the collection of the physical activity data via configuration in Actigraph system (ie, Actigraph CentrePoint). Detailed information will be included in User Manual and training for Actigraph CentrePoint for the sites.

11. ASSESSMENTS

EORTC-QLQ-C30

The EORTC-QLQ-C30 is a 30-item questionnaire to evaluate cancer patients' QOL, and it's composed of five multi-item functional subscales (physical, role, emotional, cognitive , and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL. Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant. The linguistic and psychometric validation of the questionnaire into Japanese was conducted and Japanese translated version is available with EORTC copyright.

One of the primary objectives of this study is to evaluate the change in PRO using smartphone-based application. EORTC-QLQ-C30 will be utilized in this study as PRO questionnaire. This instrument was chosen because EORTC-QLQ-C30 is disease-specific questionnaire developed for cancer patients, evaluated in clinical trials for palbociclib, and the items in social functioning in EORTC-QLQ-C30 can assess impacts on social activities and family life.

Physical Activity Metrics

Another primary objective of this study is to evaluate the change in physical activity using wearable device. Actigraph Centrepoint Insight Watch will be utilized in this study. This device was chosen due to a combination of factors, including metrics reported (eg, sedentary time, steps), validity of the device and selected metrics, availability of raw signal open to any valid algorithms for future processing, and >30-day battery life.

PRO-CTCAE

The PRO-CTCAE is a PRO measurement system that includes a library of questions that measure symptomatic adverse events from the patient perspective. Seventy-eight symptom terms that are common in oncology clinical trials can be evaluable with PRO-CTCAE, and each of symptom terms is assessed relative to one or more distinct attributes, including frequency, severity, and/or interference with usual or daily activities. Responses are provided on a five-point Likert scale. The linguistic and psychometric validation of the questionnaire into Japanese was conducted and Japanese translated version is available through US-NCI webpage.

Fatigue and General pain will be evaluated in this study. Fatigue is one of common adverse event observed in PALOMA studies, and General pain is one of the major symptoms for patients with ABC. Also, it is reported that these two symptoms are frequently underestimated, then these two are selected to evaluate in this study to understand day-to-day effects of ABC treatment on patients in a real-world setting.

Treatment satisfaction

Treatment satisfaction will be evaluated with single item question (eg, "How satisfied are you with your current breast cancer treatment?"). Responses are provided on a five-point Likert scale. Single item question is selected rather than validated questionnaire (eg, Cancer Therapy Satisfaction Questionnaire) considering the burden on patient regarding a number of questions.

12. DATA ANALYSIS/STATISTICAL METHODS

12.1. Study size

The current enrollment target for this study is 100 patients across multiple centers in Japan. This is an observational study designed to provide descriptive summary information and is not designed for hypothesis testing. The number of patients was chosen on a practical basis.

12.2. Data management

The EDC system that will be used to capture study data at the site (eCRFs) is the Oracle InFORM. The EDC system will be used to collect, monitor, and report clinical data as specified in the protocol. Investigators or study site staff will enter clinical data into the EDC system at baseline, during the observational period, and at the end of study. All data collected via the eCRF will be reviewed by remote data managers for clarity and completeness. Missing or unclear data will be queried according to the data management plan. The database and data management plan, describing data systems used, data sources, data cleaning procedures, and data transfer procedures, will be generated according to approved specifications.

Patient-reported outcome data will be captured using the mobile application designed, programmed, and hosted by PRO vendor. Physical activity data will be captured using Actigraph CentrePoint Insight Watch, designed, programmed, and hosted by Actigraph. Physical activity data will be uploaded from each patients' device to the Actigraph CentrePoint cloud system during each site visit.

Data in those systems (ie, EDC, PRO application system and Actigraph CentrePoint) will be reviewed by remote data managers for data entry and compliance. Patient-reported data and physical activity data will be transferred to clinical data management system on regular basis according to the data management plan.

Pfizer will extract all the data sets (ie, eCRF data, patient-reported data and physical activity data) and release for analysis.

12.3. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF/DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF/DCT is required and should be completed for each included subject. The completed original CRFs/DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs/DCTs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs/DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs/DCTs are true. Any corrections to entries made in the CRFs/DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs/DCTs must match those charts.

In some cases, the CRF/DCT may also serve as the source document. In these cases, a document should be available at the investigator site, JBCRG and at Pfizer that clearly identifies those data that will be recorded on the CRF/DCT, and for which the CRF/DCT will stand as the source document.

12.4. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs/DCTs and hospital records), all original signed informed consent documents, copies of all CRFs/DCTs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Council for Harmonisation (ICH), local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 5 years after completion completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12.5. Data analysis

For the purpose of this study, analyses will generally be descriptive in nature and will be conducted. All analysis will be summarized separately by groups except for the between group comparison. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by JBCRG and Pfizer. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

All variables will be summarized descriptively through tabular displays of mean, median, ranges and standard deviations of continuous variables and frequency distributions of categorical variables by measured points.

12.5.1. Primary endpoints

- As primary analysis of EORTC-QLQ-C30, change in “Global health status scale” from baseline is summarized at each measurement time point. The mean, the 95% confidence interval for the mean, and the standard deviation are calculated. Baseline values are those measured between enrollment and the day before treatment start.
- Physical activity metrics are averaged at weekly basis. As primary analysis of physical activity, change in “Sedentary time” from baseline is summarized at weekly basis. The mean, the 95% confidence interval for the mean, and the standard deviation are calculated. Baseline values are the average number between enrollment and the day before treatment start.

12.5.2. Secondary endpoints

Analysis of EORTC-QLQ-C30 scores

- The same analysis for other 14 scales of EORTC-QLQ-C30 (5 functional scales [physical, role, emotional, cognitive , and social functioning], 8 symptom scales [fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea], and financial difficulties scale) are performed as for global health status.

- Following analyses of 5 functional scales and Global health status scale of EORTC-QLQ-C30 are performed to assess the associations as follows:
  - ✓ Tabulate patients with and without selected investigator-reported AE at each cycle, summarize the mean values of change in EORTC-QLQ-C30 from baseline at each cycle in each tabulated population, and compare the results at Cycle 1 and Cycle 3 using t-test
  - ✓ Tabulate patients with and without symptom of PRO-CTCAE at each cycle, summarize the mean values of change in EORTC-QLQ-C30 from baseline at each cycle in each tabulated population, and compare the results at Cycle 1 and Cycle 3 using t-test
  - ✓ Tabulate patients with disease progression during the observation period, and summarize the mean values of EORTC-QLQ-C30 before and after disease progression

Analysis of physical activity metrics

- The same analysis for other physical activity metrics (eg, steps) is performed as for Sedentary time.
- The similar analyses of each physical activity metrics, as same as that for EORTC-QLQ-C30, are performed to assess the associations.

Association between EORTC-QLQ-C30 and Physical activity

- The Pearson's correlations between change in PRO and physical activity metrics will be calculated at each measurement time point.

Patient satisfaction

- Patient satisfaction will be summarized descriptively through tabular displays of mean, median, ranges and standard deviations of continuous variables and frequency distributions of categorical variables, by measured points.

Adverse events and PRO-CTCAE

- Investigator-reported AE and patient-reported AE will be summarized.
- Association between investigator-reported AE and patient-reported AE will be assessed using contingency table and weighted Kappa coefficient.

Feasibility of the measures

- The number of responses from EORTC-QLQ-C30 and the number of physical activity data are summarized at each measurement point
- Time from enrollment to discontinue wearing the device (ie, Time-to-wearable failure) is calculated, and the cumulative rate curve, median, and proportion of time-point continuation are estimated using the Kaplan-Meier method

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12.5.4. Missing data

Detailed methods for handling missing data will be described in the SAP.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Site training

Investigators and study site staff will be trained with an initial on-site training session and/or investigator meeting on the protocol, EDC system (eCRF), smartphone-based application (ePRO), wearable device, documentation, and any applicable study processes. Any new information relevant to the performance of this study will be forwarded to the study site staff during the study.

13.2. Monitoring

This study will be investigated based on data entered in CRF whether the study is conducted safely and according to the protocol and data are collected accurately. In principle, monitoring will be centrally performed and on-site monitoring will be conducted as needed.

13.3. Audit

To ensure the ethics of patients participating in the study and to improve the quality of clinical studies, audit may be conducted to confirm whether the study is conducted in accordance with the ethical guidelines for medical and health research in humans, the Declaration of Helsinki, the protocol and standard operating procedures, etc. Auditor will conduct an audit at the time and frequency considered the most appropriate such as at the start of the study, during the study, at the end of the study, at the study data entry, data analysis, and the completion of clinical study report, if required.

13.4. Data transfers

Data transfers between Pfizer and JBCRG will be described in a detailed Data Transfer Plan. At the end of the study, Pfizer will transfer their complete data set to the vendor for data analysis, which will combine the data sets, for data analysis. Of note, transferred data may be used for scientific research and promotion of public health in other projects.

13.5. Data quality assurance

All applicable SOPs and data-cleaning procedures will be followed with the aim of removing errors and inconsistencies in the data that would otherwise affect the analysis or credibility of the final study report.

14. LIMITATIONS OF THE RESEARCH METHODS

Considering the nature of real-world observational study, the study has the potential for missing, inaccurate, or incomplete data. Especially, as this study require patients to self-report outcomes and behavior, completeness and accuracy of reporting can be a concern. The limitations of the observational nature can result in methodological challenges in attributing causality to outcomes. Hence, this study is intended for hypothesis generation as opposed to hypothesis confirmation.

The patient selection and the diagnostic or monitoring procedures are those applied per the usual treatment paradigm of the treating physician and not dictated by the protocol. Heterogeneous patient populations could make the interpretation of the outcomes difficult.

As this study will collect PRO data via smartphone-based application, participating patients must own and have regular access to smartphone; thus, the study population may not be representative of the ABC population, which may include technology- or mobile device-naive patients.

As the data collection period for each patient is 6 months, feasibility of ePRO and wearable device (ie, ePRO data entry and wearing period) can be a concern.

Although it is easily understood by general public, Steps is not well validated with wrist watches and sometimes underestimated. Therefore, Sedentary time is also evaluated to assess the impact of ABC treatment on patients' physical activity.

15. PROTECTION OF HUMAN SUBJECTS

15.1. Patient Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data on any sponsor forms, reports, publications, or in any other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in *encrypted electronic* form and will be *password protected* to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data

breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer, JBCRG and other authorized parties, subject names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, JBCRG and Pfizer will maintain high standards of confidentiality and protection of subject's personal data consistent with the clinical study agreement (CSA) concluded among Pfizer, JBCRG and investigator site and applicable privacy laws.

The informed consent documents must be in compliance with local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by Pfizer, approved by the IRB/EC before use.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document. If the subject and the relevant person have consulted, the investigator or the study staff of each study site will respond.

15.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator, in consultation with Executive committee of this study if needed, for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if applicable. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events until the event resolve or stabilize at a level acceptable to the investigator.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. JBCRG and Pfizer may retain and continue to use any data collected before such withdrawal of consent.

15.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to JBCRG office and Pfizer.

The investigator must obtain IRB/IEC review and approval for the continuation of the study at least once a year. For annual contract renewal, the standard procedure of each institution shall be followed.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

15.4. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare (MHLW), and the Declaration of Helsinki.

16. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS REQUIREMENTS

This study includes qualifying diagnostic or monitoring procedures required per protocol to collect clinical data needed to meet the study objectives, which are not standard-of-care but that do not pose more than a minimal risk or burden to the study subject. The qualifying procedure in this study is physical activity data collection using wearable device.

16.1. Adverse Events (AE)

An AE is defined as any untoward medical occurrence and can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not related to the subject's participation in the study.

AE reporting period for each subject begins from the time the subject provides informed consent, through the end of the observation period of the study which must include at least 28 calendar days following the last administration of the drug under study. **Any AE related to**

above procedure that occurs from the time the subject consents to the clinical research through and including 12 hours after completion of the qualifying procedure must be recorded. The investigator is required to assess whether the AE may be related to the subject's participation in the study. All AEs (ie, serious and non-serious, including those attributed to qualifying procedure identified as research-related injury) are collected in the clinical study database.

The investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a research-related injury requiring immediate notification to Pfizer as described below.

16.2. Research-Related Injury

Should a subject, in the investigator's opinion, suffer a medically important research-related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately.

A medically important research-related injury is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research-related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Formto Pfizer Safety. These requirements are delineated for four types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); (3) scenarios involving drug exposure during pregnancy or breast feeding, and occupational exposure; and (4) scenarios involving medication errors. These events are defined in the section "Definitions of safety events". Of note, treatment for advanced breast cancer administered within the observation period of this study (ie, palbociclib plus endocrine therapy or endocrine monotherapy) is described as "drug under study".

Safety event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety within 24 hours of awareness**
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) **Note:** Any serious associated adverse event is reported together with the exposure scenario. For occupational exposure, both serious and non-serious AEs are reported

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator are to be reported regardless of whether the event is determined by the investigator to be related to the drug under study. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include

a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

16.2.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

16.2.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

16.2.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

16.2.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving the marketed product under study), through the end of the

observation period of the study which must include at least 28 calendar days following the last administration of the drug under study.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

16.2.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to drug under study must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

16.2.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs and research-related injury due to wearable device must continue to be recorded on the CRF during the above-indicated active collection period.

16.2.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the drug under study caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the drug under study caused the event, then the

event will be handled as “related to drug under study” for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is “unknown but not related” to drug under study, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

16.2.6. Sponsor’s Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

16.3. Definitions

16.3.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.
- Additionally, AEs may include signs and symptoms resulting from:
- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

16.3.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

16.3.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

16.3.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).
- Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

16.4. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with

the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

16.5. Special Situations

16.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

16.5.2. Exposure to the Drug under study During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the drug under study under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

16.5.2.1. Exposure During Pregnancy

For marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the drug under study; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the drug under study;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
2. A male has been exposed (eg, because of treatment or environmental exposure) to the drug under study prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the drug under study, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the drug under study.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

16.5.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

16.5.2.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE.

When the occupational exposure is associated with an adverse event, it is reported to Safety regardless of the seriousness criterion associated with that adverse event.

Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

16.5.3. Medication Errors

Other exposures to the drug under study may occur in studies, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors may result from the administration or consumption of the drug under study by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the drug under study;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if

applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

16.6. Single reference safety document

The Japan package insert for drug under study including palbociclib will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

17. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

17.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the drug under study, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

17.2. Publications by Investigators

Study results will be presented at appropriate scientific meetings and reported as papers. Caution will be exercised in protecting the confidentiality of personal information when making presentations. After the publication of the primary results, study site may use the study results obtained from each study sites. However, if information on the present research (including the introduction of the study and case report, etc.) is presented externally, the purpose and content of the presentation (including the date, time, place, title, presenter, and abstract, etc.) should be notified to Executive committee of this study and the approval should be obtained before the submission. Any patent or other intellectual property rights arising from the results of this study are determined by JBCRG and Pfizer after discussion.

This study will be registered in the ClinicalTrials.gov, etc. and the information will be disclosed. The registration shall be performed by the principal investigator, JBCRG office and/or Pfizer.

18. PAYMENT FOR COOPERATING THE STUDY AND COMPENSATION FOR RESEARCH RELATED INJURY

18.1. Payment for study participant

The contents of medical care in this study are similar to those in usual medical care. The treatment in this study is performed at the range of daily medical care using drugs already approved. Therefore, all medical expenses including drugs and investigations during the study period will be covered by public health insurance and the patient's own copayment. In order to reduce the burden on participation in this study, patients will be paid 20,000 yen or an equivalent amount of gift voucher for study participation upon completion or discontinuation of the study.

18.2. Compensation

If an adverse event occurs during the study, the investigator will promptly take necessary measures (investigation, treatment, and study discontinuation) to ensure the safety of the study participants. In such case, the best medical care within the range of public health insurance treatment shall be provided. Compensation will be made for injury associated with the procedures required for participation in this study (ie, wearing of wearable device). However, compensation will not be made for other injury. Investigator shall take necessary measures such as insurance for indemnification before the start of this study in preparation for liability.

18.3. Burden, risk and benefit associated with study participation

All drugs used in this study have been approved for the indication, and all treatments will be covered by public health insurance. All medical expenses including drug expenses during the study will be covered by public health insurance and the patient's own copayment. Therefore, there is no economic benefit to patients from taking part in this study compared to routine clinical practice (excluding the above-mentioned payment for study participants). Disadvantages include the occurrence of adverse events observed in clinical studies conducted to date, and in some cases, treatment-related death. However, this can also happen in routine clinical practice, and it does not change because of participation in the present research.

19. SPECIAL NOTES

19.1. Conflict of interest

Any potential conflicts of interest in the planning, conduct, and publication of this study will be disclosed. Conflict of interest refers to an interest that may affect study results, including financial and personal relationships. Since this study is a multicenter study, each investigator's conflicts of interest are managed by each study site.

19.2. Source of research funding

This study will be conducted with Pfizer funding.

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21. LIST OF TABLES

None

22. LIST OF FIGURES

23. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Appendix 1. Contact details of responsible parties and all investigators

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