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PALLAS: PALbociclib CoLlaborative Adjuvant Study:
A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

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PROTOCOL SIGNATURE PAGE

PALLAS Site ID: _ _ _ _ _ _

Protocol Title: **PALLAS**: **PAL**bociclib **C**o**L**laborative **A**djuvant **S**tudy:
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Protocol Number: AFT – 05, ABCSG 42, BIG 14-03
EudraCT Number: 2014-005181-30

US Sponsor Name: Alliance Foundation Trials (AFT), LLC
Non-US Sponsor Name: ABCSG GmbH

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, all applicable regulations, ICH Good Clinical Practice (GCP) and Declaration of Helsinki.

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First Name, Last Name Date, Signature

I. Synopsis

Study Title	**PALLAS**: **PAL**bociclib Co**L**laborative **A**djuvant **S**tudy: A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer
Study Code	AFT-05, ABCSG-42, BIG 14-03
EudraCT Number	2014-005181-30
IND Number	126003
Sponsor	AFT (US), ABCSG GmbH (Non-US Sites)
Extended Academic Core Network	BIG, GBG, NSABP, PrECOG
Phase	Phase III
Rationale	Although many patients with HR+/HER2- breast cancer may be cured of their disease with optimal local and systemic therapy, a significant number of patients with stage II and III disease will experience disease recurrence. Adjuvant endocrine therapy for breast cancer can be extremely effective, particularly with extension beyond 5 years, however disease recurrence can occur, with risk distributed over the decades following initial diagnosis. Methods to improve the efficacy of endocrine therapy, and delay the onset of resistance, are needed. HR+ breast cancer biologically may demonstrate features suggestive of sensitivity to CDK4/6 inhibition with agents such as palbociclib. Given the demonstrated activity and safety of palbociclib in the first-line treatment of metastatic HR+/ HER2- breast cancer, supporting FDA approval, there is interest in whether the benefits of CDK4/6 inhibition may translate into the adjuvant setting. The purpose of the PALLAS study is to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR+/HER2- early breast cancer. Assessment of a variety of correlative analysis, including evaluation of the effect of palbociclib in genomically defined tumor subgroups, is planned.
Primary Objective	To compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment versus at least 5 years endocrine therapy alone in patients with histologically confirmed HR+/HER2- invasive early breast cancer (EBC).

Secondary Objectives	To compare the following endpoints: iDFS excluding second primary invasive cancers of non-breast origin, distant recurrence-free survival (DRFS), locoregional recurrences-free survival (LRRFS), and overall survival (OS). To compare the safety of 2 years of palbociclib with adjuvant endocrine therapy versus adjuvant endocrine therapy alone.
Translational Science Principal Objective	To compare baseline tumor tissue to determine whether there is prognostic or predictive utility for defined genomic subtypes (luminal A, luminal B and non-luminal) with respect to iDFS and OS.
Translational Science Additional Objectives	To evaluate iDFS and OS in other genomically-defined breast cancer prognostic, theranostic or predicted subgroups based on pre-specified genomic assays. To evaluate baseline tumor and blood-based markers as predictors of benefit from the addition of palbociclib to endocrine therapy. To evaluate tumor and blood-based markers at time of disease recurrence for mechanisms of resistance to palbociclib and endocrine therapy. To perform exploratory analyses of serum and plasma samples over time to investigate the predictive and prognostic value of novel biomarkers in this specific trial setting related to efficacy or safety of the agent. To compare serial levels of circulating cell-free DNA (cfDNA) in patients receiving palbociclib and endocrine therapy versus endocrine therapy alone. To evaluate pharmacogenomic and pharmacogenetic predictors of toxicity and efficacy of palbociclib and endocrine therapy and to endocrine therapy alone.
Clinical Science Objectives	To evaluate adherence to oral therapy in patients receiving palbociclib and endocrine therapy. To determine the association of BMI with the efficacy of palbociclib and endocrine therapy.
Patient Reported Outcome Objective	To compare patient-reported quality of life, fatigue, arthralgia, alopecia, menstrual function, and endocrine symptoms of HR+/HER2- breast cancer patients randomized to receive palbociclib plus adjuvantstandard endocrine therapy versus standard endocrine therapy aloneoverall and by subgroups defined by age at randomization (≤50 and >50) and initial endocrine therapy (tamoxifen and AI) at multiple pre-specified time points.

Trial Design and Schema	This is a prospective, two arm, international, multicenter, randomized, open-label Phase III study evaluating the addition of 2 years of palbociclib to standard adjuvant endocrine therapy for patients with HR+ / HER2- early breast cancer (EBC). **Schema** Randomized, open-label, Stage II or III EBC Patients (Stage IIA limited to 1000 patients).

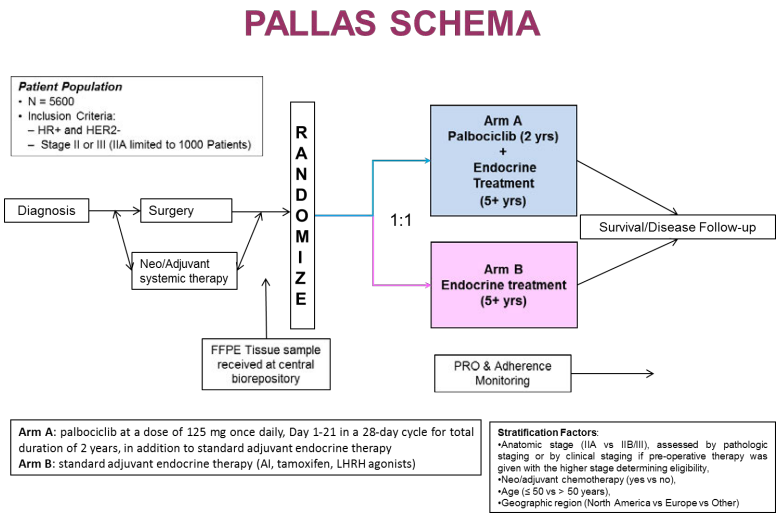

Figure 1: *PALLAS Study Schema*

Endocrine adjuvant therapy may have started before randomization and be ongoing at the time of randomization.

Eligible patients will be receiving standard adjuvant endocrine therapy for HR+/ HER 2- early breast cancer. A total of 5600 patients (revised target accrual) will be randomized in a 1:1 ratio to:

> **Arm A**: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy for a duration of at least 5 years.
> **Arm B**: standard adjuvant endocrine therapy for a duration of at least 5 years.
>
> Standard endocrine therapy (also referred to as background treatment) can be tamoxifen or aromatase inhibitor with or without LHRH agonist.

	Patients will be randomized within strata defined by: • Anatomic stage (IIA vs IIB/III) assessed by pathologic staging, or by clinical staging if pre-operative therapy was given with the higher stage determining eligibility, • Neo/adjuvant chemotherapy (yes vs no), • Age (≤ 50 vs > 50 years), • Geographic region (North America vs Europe vs Other) Patients randomized into Arm A will receive protocol-assigned palbociclib therapy for the planned duration of 2 years or until diagnosis of an iDFS event, unacceptable toxicity, patient withdrawal of consent, or study termination by the Sponsor, whichever occurs first.
Inclusion Criteria	Please note that waivers to eligibility requirements are not allowed. **Patients must meet the following criteria for study entry** **(1)** Signed informed consent obtained prior to any study specific assessments and procedures. **(2)** Age ≥18 years (or per national guidelines). **(3)** Premenopausal and postmenopausal women or men with Stage II (Stage IIA limited to a maximum of 1000 patients) or Stage III early invasive breast cancer per AJCC (American Joint Committee on Cancer) Breast Cancer Staging version 7 /UICC (Union for International Cancer Control)[54]. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT, is at the discretion of theinvestigator. If neoadjuvant systemic therapy was received (either chemotherapy or endocrine therapy or biologic therapy excluding 'Anti-HER2 treatment'), either initial clinical stage (determined by physical and/or radiologic examination) or post-operative pathologic stage can be used for eligibility purposes, with the higher stage determining eligibility. **(4)** Patients with multicentric and/or multifocal and/or bilateral early invasive breast cancer whose histopathologically examined tumors all meet pathologic criteria for ER+ and/or PR+ and HER2-. **(5)** Patients must have histologically confirmed

	hormone receptor positive (ER+ and/or PR+),HER2-, early invasive breast cancer. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA- approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines[55, 95]. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment. Testing may occur on diagnostic core or surgical tumor tissue. **(6)** Patients must have undergone adequate (definitive) breast surgery for the current malignancy. For details please refer to Appendix D. **(7)** A formalin-fixed paraffin-embedded (FFPE) tumor tissue block must be transmitted to a central sample repository and confirmation of receipt must be available prior to randomization. For details please refer to Section 8.2 of the protocol. **(8)** ECOG performance status 0-1. **(9)** Patients must be able and willing to swallow and retain oral medication without a condition that would interfere with enteric absorption. **(10)** Serum or urine pregnancy test must be negative within 7 days of randomization in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. Women of childbearing potential and male patients randomized into treatment Arm A or B must use adequate contraception for the duration of protocol treatment and for 6 months after the last treatment with palbociclib if they are in arm A. In addition, patients receiving standard adjuvant endocrine therapy (Arm A and Arm B) should use adequate contraception in accordance with the specific medication requirements (e.g. Summary of Product Characteristics). Adequate contraception is defined as one highly effective form (i.e. abstinence*, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

	*Abstinence is to be interpreted as "true abstinence" for heterosexual intercourse and therefore, "periodic abstinence" (e.g. calendar, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not considered highly effective. Prior Treatment Specifics **(11)** Patients may or may not have received neo/adjuvant therapy, but must be after last dose of chemotherapy and/or biologic therapy and must have sufficient resolution of side effects per physician assessment at the time of randomization. **(12)** Patients may or may not have received breast/axilla/post-mastectomy chest wall radiotherapy, but must be after last dose of radiotherapy and must have sufficient resolution of side effects per physician assessment at the time of randomization. **(13)** Patients must have sufficient resolution of any surgical side effects from the last surgery per physician assessment with no active wound healing complications at the time of randomization. **(14)** Patients must either be initiating or have already started **adjuvant hormonal treatment**. Patients may already have initiated endocrine therapy at the time of randomization, but randomization must take place within 12 months of date of histological diagnosis and within 6 months of initiating standard adjuvant endocrine therapy. Patients who received **neoadjuvant endocrine therapy** are eligible as long as they are randomized within 12 months of initial histological diagnosis and after completing no more than 6 months of adjuvant endocrine therapy. Patients may be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients and men, concurrent LHRH agonist use is allowable and may also be ongoing at the time of randomization. If a LHRH agonist was used for ovarian protection during neo/adjuvant chemotherapy it is allowable and shall not be taken into account for calculations regarding the 6 months standard adjuvant endocrine therapy. Baseline Body Function Specifics **(15)** Absolute neutrophil count $\geq 1{,}500/mm^3$ **(16)** Platelets $\geq 100{,}000/mm^3$ **(17)** Hemoglobin $\geq$ 10g/dL **(18)** Total serum bilirubin $\leq$ ULN; or total bilirubin

	≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome. **(19)** Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 1.5 × institutional ULN. **(20)** Serum creatinine below the upper limit of the institutional normal range (ULN) or creatinine clearance (or glomerular filtration rate [GFR]) ≥ 60 mL/min/1.73 m^2 for patients with serum creatinine levels above institutional ULN.
Exclusion Criteria	**Patients who meet any of the following criteria will be excluded from study entry:** **(1)** Concurrent therapy with other Investigational Products. **(2)** Prior therapy with any CDK inhibitor. **(3)** Patients with Stage I or IV breast cancer are not eligible. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT, is at the discretion of the investigator. **(4)** History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib. **(5)** Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization (see Section 9.5.2.1 of the protocol for list of CYP3A inhibitors and inducers). **(6)** Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation. **(7)** Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization,

	irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry. **(8)** Patients with a history of any malignancy are ineligible except for the following circumstances: • Patients with a malignancy history other than invasive breast cancer are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. • Patients with the following cancers are eligible, even if diagnosed and treated within the past 5 years: ductal carcinoma *in situ* of the breast, cervical cancer *in situ*, and non- metastatic non-melanomatous skin cancer. **(9)** Patients are not eligible if they have previously received endocrine therapy within 5 years prior to diagnosis of the current malignancy. This includes use for prophylactic reasons, including treatment of osteoporosis or cancer prevention with tamoxifen, raloxifene or AI. Patients may concurrently receive bisphosphonates or rank ligand inhibitors while on this study if necessary for treatment or prevention of osteopenia or osteoporosis. **(10)** Patients on antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib. **(11)** Patients with clinically significant history of chronic liver disease, including chronic/active viral or other known hepatitis, current alcohol abuse, or cirrhosis, etc. **(12)** Patients receiving concurrent exogenous hormone therapy (hormone replacement therapy, oral or any other hormonal contraceptives such as hormonal contraceptive coil, etc.) are not eligible but topical vaginal estrogen therapy is allowable.
Investigational Product and Formulation	Palbociclib at a dose of 125 mg will be administered orally once a day, at the same time, for 21 days, followed by 7 days off treatment of every 28-day cycle. Investigational medicinal product (IMP) will be administered with standard adjuvant endocrine therapy (Non-investigational product).

Non-investigational Treatment and Formulation	Current treatment guidelines recommend adjuvant endocrine treatment for 5 to 10 years after surgery for patients with hormone-receptor-positive disease. Adjuvant endocrine treatment might have already started before the patient enters the study, however, initiation of standard adjuvant endocrine therapy must not be more than 6 months before randomization (please refer to inclusion criterion 14). The following endocrine therapies are allowed: • tamoxifen • non-steroidal aromatase-inhibitors (anastrozole, letrozole) • steroidal aromatase inhibitor (exemestane) • LHRH agonists in combination with tamoxifen or AI for premenopausal women and men
Analysis Populations	**ITT Population:** We will use intention to treat (ITT) principles to define the population used for the analysis of the primary endpoint and secondary efficacy endpoints. The ITT Population is comprised of all randomized patients, including those who do not start palbociclib or endocrine treatment. This population provides the basis for the main efficacy analyses. Patients will be analyzed according to the treatment group to which they were randomized. Randomized patients consist of all patients who have given their written informed consent and forwhom there is confirmation of successful allocation of a randomization number through the IxRS (Interactive Voice and Web Response System). **Safety Population (SP):** For the purposes of evaluating and monitoring Adverse Events and all other patient safety, the Safety Population (SP) is defined as all randomized patients, excluding those who do not start palbociclib or endocrine treatment, i.e. as-treated. Patients will be analyzed according to treatment actually received. Randomized patients for whom it is unclear whether they took the palbociclib or endocrine treatment will be included in the safety population as randomized.
Sample Size Calculation	The revised total accrual is 5600 patients. A maximum of 1000 Stage IIA patients are to be enrolled. If the maximum is reached, the studywill proceed to enroll only Stage IIB and III patients. Sample size is based on a target effect size on the hazard ratio (HR) scale for Arm A over Arm B of 0.75 as a clinically relevant level of improvement in iDFS. To have 85% power to detect this difference after accounting for interim analyses plans, the final analysis will occur when 469 iDFS events are observed. <u>Original assumptions:</u> Total accrual is determined based on the assumed iDFS for patients on Arm B (standard adjuvant endocrine therapy; control) using resultsfrom ECOG 5103: Phase 3 randomized study of adjuvant therapy comprising doxorubicin hydrochloride, cyclophosphamide, and paclitaxel with versus without bevacizumab in patients with lymphnode-positive or high-risk, lymph node-negative breast cancer[48]. In the

	ER+ subset, the 5-year iDFS rate was 0.74, 0.82, and 0.92 for Stages III, IIB, and IIA, respectively. By simulation, it is anticipated that the 5-year iDFS rate will be 0.81 in Arm B for a mixed patient populationwith 39% Stages III, 39% IIB and 22% IIA patients (capped). To define the total sample size, it is assumed that time to iDFS event and time to dropout follow an exponential distribution. The dropout rateis assumed to be 10% at 5 years. Assuming a quarterly step-wise increase in enrollment over the first year, and a constant rate of 153 patients per month thereafter, 4600 patients will be enrolled within 36 months. The final analysis at 469 iDFS events is anticipated to occur after 22 months of additional follow-up. <u>Revised assumptions:</u> The first patient was randomized in September 2015, and enrollment reached the cap of 1000 Stage IIA patients in September 2017 and closed to further accrual of this patient cohort. As of February 2018, over 3500 patients have been enrolled into the study, with the rate of recruitment exceeding 250 during January 2018. The recruitment periodis therefore anticipated to be shorter than originally projected. Further, contemporary trials investigating adjuvant treatment of hormone receptor-positive breast cancer have shown improved clinical outcomes and lower event rates. Specifically, in NSABP B-47 the 5-year iDFSrate was 0.896 and 0.892 with and without the addition of trastuzumab to standard adjuvant therapy, respectively. In ABCSG-18, a randomizedplacebo-controlled study of the addition of denosumab to standard adjuvant AI therapy (n = 3425), the 5-year iDFS rate was 0.78, 0.85, and 0.89 for Stages III, IIB, and IIA, respectively. In TEXT, premenopausal women received ovarian function suppression with anti-estrogen therapy and 5-year iDFS rate was 0.77, 0.87, and 0.92 for Stages III, IIB, and IIA, respectively. Under an exponential model, the hazard ratio of iDFS in TEXT relative to the control arm of ECOG 5103is 1.15, 1.42 and 1.0 for Stages III, IIB, and IIA, respectively, and supports an additional 1000 patients that are stage III or IIB, such that the study population is expected to be 41% Stages III, 41% IIB and 18% IIA patients (capped at 1000 patients). A revised total sample size of 5600 is anticipated to be enrolled within 41 months. By simulation using (a) the actual accrual through 2017 and constant accrual thereafter, (b) the 5-year iDFS rates for stage IIB and III observed in TEXT, and (c) the original dropout rate of 10% at 5 years, the final analysis at 469 iDFS events is anticipated to occur after 24 months of additional follow-up (65 months total). Power is also calculated for the secondary endpoint: iDFS excluding second primary invasive cancers of non-breast origin as an event. Under the assumption that 12% of iDFS events will be second primary invasive cancers of non-breast origin, and time to event for this endpoint will follow an exponential distribution, there will be a 79.3% power to detect a HR = 0.75 for the secondary endpoint of iDFS excluding second primary invasive cancers of non-breast origin using a

	one-sided alpha = 0.025. The expected study duration to primary analysis of iDFS is 5.4 years.
Interim Monitoring and Interim Analysis	Two interim efficacy analyses are planned for monitoring for futility and superiority, and are scheduled to occur when 33% and 67% of the total number of iDFS events are observed. **The first interim analysis** will take place after the first 157 iDFS events have occurred and the second interim analysis will take place after accrual is completed and 313 iDFS events have occurred. Under original assumptions: It is estimated that the 1st interim analysis will occur <3 years and the 2nd interim analysis will occur <4 years after the first patient is randomized. Under revised assumptions: the 1st interim analysis is expected to occur <4 years and the 2nd interim analysis to occur <5 years after the first patient is randomized. The objective of the first interim efficacy analysis will be: • To assess safety. • To allow for early stopping of the trial due to futility. • To consider re-estimation of total sample size. The objective of the second interim efficacy analysis will be: • To assess safety. • To allow for early stopping of the trial due to futility. • To allow for early stopping of the trial due to overwhelming efficacy (superiority stopping boundary is crossed). • To consider re-estimation of total sample size. Although stopping the trial for overwhelming efficacy (superiority stopping boundary is crossed) is not considered as one of the objectives at the first interim analysis, the nominal alpha for the first interim analysis is still taken into account when calculating overall type I error. The following table summarizes the nominal significance level, corresponding hazard ratio, and 3-year and 5-year iDFS rates for each arm at the 2nd interim analysis and the final analysis when 67% of total events (313 events) or 100% of total events (469 events) are observed. The corresponding hazard ratio is estimated under the assumption of proportional hazards, and the corresponding 3-year / 5-year iDFS rates are estimated under the assumption of exponential distribution for iDFS.

Analysis	Nominal α level (1-sided)	Estimated Hazard ratio	Estimated 3-year iDFS rate for		Estimated 5-year iDFS rate for	
			Control arm	Palbo-ciclib arm	Control arm	Palbo-ciclib arm
Original assumptions						
2nd interim analysis	0.006	0.753	0.881	0.909	0.81	0.853
Final analysis	0.0231	0.832	0.881	0. 900	0.81	0.839
Revised assumptions						
2nd interim analysis	0.006	0.753	0.897	0.923	0.835	0.876
Final analysis	0.0231	0.832	0.897	0.915	0.835	0.863

At each interim efficacy analysis, statistical hypothesis tests will be performed only for the primary efficacy endpoint, iDFS and the secondary endpoint, iDFS excluding second primary invasive cancer of non-breast origin. O'Brien – Fleming type stopping boundaries[58] based on the Lan-DeMets spending function will be applied. Futility criteria will not be used to calculate the nominal alphas in order to control the overall Type I error (non-binding method). The Z-statistic from a one-sided, stratified logrank test will be calculated and compared to the stopping boundaries, and are defined on the Z-statistic scale for formal comparison to logrank test. In addition to the boundary and observed Z-statistics, the IDMC will be provided Kaplan-Meier product limit estimators to the survival functions for each arm, and estimated HRs and 95% CIs from the corresponding Cox proportional hazard models for iDFS.

The IDMC will also be provided estimates (Kaplan-Meier, HR and 95% CI) for the secondary endpoint, iDFS excluding second primary invasive cancer of non-breast origin.

Decision rules for sample size re-estimation at the first and second interim analyses will be based on the Cui, Hung and Wang[61] method using conditional power based on the point estimate and standard error for the HR. Details on the sample size re-estimation and modifications to the stratified log-rank test to control the overall Type I error will be provided in the Statistical Analysis Plan (SAP).

II. Table of contents

1. Background 22
1.1. Rationale for Patient Population: Hormone Receptor Positive Breast Cancer 22
1.2. Palbociclib Mechanism of Action 22
1.3. Palbociclib Preclinical Data 23
1.4. Palbociclib Pharmacokinetic (PK) Data in Humans 24
1.5. Palbociclib Clinical Data 29
1.6. Clinical Safety Overview for Palbociclib 31
1.7. Palbociclib and Endocrine Therapy Pharmacokinetics 33
1.8. Study Rationale 35
2. Objectives 39
2.1. Primary Objective 39
2.2. Secondary Objectives 39
2.3. Translational Science Principal Objective 39
2.4. Translational Science Additional Objectives 40
2.5. Clinical Science Objectives 40
2.6. Patient-Reported Outcomes Objective 40
2.7. Endpoints 40
3. Study Design 41
3.1. Overall Description of Study Design 41
4. Patient Selection 43
4.1. Inclusion Criteria 43
4.2. Exclusion Criteria 45
5. Method of Treatment Assignment/Patient Randomization 46
5.1. Site Enrollment Requirements 46
5.2. Patient Randomization Procedure 46
5.3. Stratification Factors 47
6. Study Assessments and Procedures 47
6.1. Study Phases 47
6.2. Disease monitoring 51
6.3. Informed Consent 51
6.4. Medical History and Demographic Data 51
6.5. Reporting of Concomitant Medication 52

6.6. Physical Examination and Vital Signs 52
6.7. Laboratory Assessments 53
6.8. Adherence Measures 53
6.9. Patient Reported Outcome Measures 54
6.10. Study measures implemented during COVID-19 Pandemic 56
7. Schedule of Assessments 58
8. Data and Specimen Submission 61
8.1. Data Collection and Submission 61
8.2. Specimen Collection and Submission 62
9. Study Treatment 64
9.1. Study Treatment Overview/Terms and Descriptions 64
9.2. Palbociclib - Investigational Product (IP) 64
9.3. Endocrine Therapy - Non-Investigational Product (Non-IP) 67
9.4. Dose and Treatment Modifications 70
9.5. Concomitant Medications 77
10. End of Treatment/End of Study Visits 79
10.1. End of Treatment 79
10.2. End of Study 80
11. Safety Instructions and Guidance 81
11.1. Adverse Events – General Overview 81
11.2. Adverse Events – Reporting Period 82
11.3. Assessment of Severity of Adverse Events 82
11.4. Assessment of Causality of Adverse Events 83
11.5. Routine Adverse Event Reporting 84
11.6. Expedited Adverse Event Reporting 85
11.7. Expected Toxicities 88
11.8. SUSAR Reporting 89
12. Measurement of Effect 89
13. Statistical Considerations and Methodology 90
13.1. Overview of the Study Design 90
13.2. Endpoints 91
13.3. Analysis Populations 92
13.4. Analysis Plans for the Primary Endpoint 92
13.5. Sample Size, Accrual time, and Study Duration 96

13.6. Study Operating Characteristics 98
13.7. Analysis Plans for Secondary, Translational and PRO Endpoints 99
13.8. Correlative Science Objectives (TRANS-PALLAS) 99
13.9. Independent Data Safety Monitoring the Study 100
14. Correlative Sciences and Clinical Data Science 100
15. General Regulatory Considerations and Credentialing 101
15.1. Regulatory and ethical compliance 101
15.2. Ethics and Good Clinical Practice 101
15.3. Confidentiality 101
15.4. Protocol Amendments 102
15.5. Informed Consent 102
15.6. Financial Disclosure 103
15.7. Quality Control 103
15.8. Protocol Deviations 103
15.9. Retention of Records 104
15.10. Trial Administrative Governance Structure 104
16. References 106
17. Appendices 112
APPENDIX A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria 112
APPENDIX B: PALLAS ~ Phases for Data Collection & Follow-Up 113
APPENDIX C: AJCC Cancer Staging from Edge S, Byrd DR, Compton CC, et al. AJCC cancer staging manual (7th ed). New York, NY: Springer; 2010 114
APPENDIX D: Recommendations on adequate local treatment for PALLAS trial candidates 119

III. List of Tables

Table 1 Adverse Events From 3 Randomized Studies in Patients With HR Positive, HER2 Negative Advanced or Metastatic Breast Cancer (N=872) 32

Table 2 Schedule of Assessments 58

Table 3 Tissue/Samples for TRANS-PALLAS translational research 63

Table 4 Palbociclib capsule characteristics 64

Table 5 Study treatment administration and dosing schedule for Arm A and Arm B 69

Table 6 Palbociclib Dose Levels and Dose Reduction Schedule 74

Table 7 AE triggered Dose Modifications and Treatment Management for Arm A 75

Table 8 Adverse Event Severity Grading Scale 83

Table 9 Adverse Events - Causal Attribution Guidance 84

IV. List of Figures

Figure 1 PALLAS Schema 42

V. Abbreviations and Terms

ABC	Advanced Breast Cancer
ABCSG	ABCSG GmbH is the Austrian Breast and Colorectal Cancer Study Group (cooperative group sponsoring PALLAS outside the US)
AE	Adverse Event
AI	Aromatase Inhibitor
AFT	Alliance Foundation Trials USA (cooperative group sponsoring PALLAS in the US)
AJCC	American Joint Committee On Cancer
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferases
ALND	Axillary lymph node dissection
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferases
AUC	Area Under the Curve
$AUC_{(0-24)}$	Area under the concentration-time curve from time 0 to 24 hours after dosing
AUC_{inf}	Area under the concentration-time curve from hour 0 to infinity
BCPT	Breast Cancer Prevention Trial Symptom Scale
BCRP	Breast cancer resistance protein
BFI	Brief Fatigue Inventory

BIG	Breast International Group
BMI	Body Mass Index
BPI	Brief Pain Inventory
BSEP	Bile salt export pump
CAP	College of American Pathologists
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CDKN2A, $p16^{Ink4A}$	Cyclin-Dependent Kinase Inhibitor 2A
cfDNA	Circulating Cell-Free DNA
C	Cycle
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
COVID-19	Disease caused by SARS-CoV-2 infection, often synonymously used with such infection as well as "corona virus disease"
CRF	Case Report Form
CSF	Colony-Stimulating Factors
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
D	Day
DCIS	Ductal Carcinoma In Situ
DDFS	Distant disease-free survival
DDI	Drug-drug interaction
DFS	Disease free survival
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DRFS	Distant Recurrence-Free Survival
EBC	Early breast cancer
EC	Executive Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ER	Estrogen Receptor
FACT	Functional Assessment of Cancer Therapy
FDA	US Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
GnRH	Gonadotropin releasing hormone
Hb	Hemoglobin
HDPE	High Density Polyethylene
HER	Human Epidermal Growth Factor Receptor
HER2	Human epidermal growth factor receptor 2

HR	Hazard ratio
HR	Hormone receptor
HRQL	Health-related QOL
IB	Investigator's Brochure
IC_{50}	Concentration of 50% Inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSI	Intracytoplasmic sperm injection
iDFS	Invasive disease-free survival
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IIR	Investigator-Initiated Research
IM	Intramuscular
IP	Investigational Product; (Investigational Medicinal Product (IMP) can be used equally
IP Treatment	Adjuvant palbociclib treatment within Arm A
IRB	Institutional Review Board
IUD	Intrauterine Device
IVF	In-vitro fertilization
IxRS	Interactive Voice and Web Response System
ITT	Intent-to-treat
LCIS	Lobular Carcinoma In Situ
LFT	Liver Function Test
LHRH	Luteinizing hormone-releasing hormone
LRRFS	Locoregional recurrence-free survival
LSLV	Last Subject Last Visit
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MMAS-4	Morisky Medication Adherence Scale
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
Non-IP Treatment (also referred to as Background Treatment)	Standard adjuvant endocrine therapy within Arm A and B (according to the EU guidance document on the definition of Investigational Medicinal Products (IMPs) and Non Investigational Medicinal Products (NIMPs) [SANCO/C/8/SF/cg/a.5.001(2011)332855])
NSABP	National Surgical Adjuvant Breast and Bowel Project
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall Survival
PALLAS	PALbociclib CoLlaborative Adjuvant Study
Patient	Patient participating in the study; terms patient and subject can be used equally
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PR	Partial Response or Progesterone Receptor (depending on context)

Participating Groups and Academic Identifiers:
AFT (AFT-05), ABCSG (ABCSG 42), BIG (BIG 14-03), PrECOG (PrE0109), NSABP (B-57-I)

PR	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.
pRB	Retinoblastoma protein
PRO	Patient Reported Outcome
Provider	Anyone rendering medical care to the patient, including e.g., physicians, nurse practitioners, physician assistants, and others.
PS	Performance Status
QD	Quaque Die (once daily)
QOL	Quality Of Life
QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The QRS complex reflects the rapid depolarization of the right and left ventricles.
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT_c	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcS	QT interval corrected for heart rate according to a study-specific correction factor
RB/Rb	Retinoblastoma
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	The interval between an R wave and the next R wave
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SC	Subcutaneous
SC	Steering Committee
SD	Stable Disease or Standard Deviation (depending on context)
SmPC	Summary of Product Characteristics
SULT	Sulfotransferase
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
T_{max}	Time for C_{max}
TRC	Translational Research Committee
UICC	Union for International Cancer Control
UK	United Kingdom
ULN	Upper Limit of Normal
URTI	Upper respiratory tract infection
US	United States
USA	United States of America
V_z/F	Apparent Volume of Distribution
WBC	White Blood Cells

1. Background

1.1. Rationale for Patient Population: Hormone Receptor Positive Breast Cancer

Hormone receptor positive (HR+) breast cancer is the most commonly diagnosed subset of breast cancer, and affects thousands of patients every year[44]. Endocrine therapy is highly effective for this subset of breast cancer. Standard adjuvant management for postmenopausal women with HR+ breast cancer involves adjuvant endocrine therapy for at least 5 years, including treatment with an aromatase inhibitor. Standard treatment for women with premenopausal HR+ breast cancer can include tamoxifen with or without ovarian suppression, or AI with ovarian suppression, and is recommended for at least 5 years. Studies evaluating extended adjuvant endocrine therapy have suggested increased benefit when therapy is extended to up to 10 years. Despite this effective therapy, a percentage of patients will relapse with incurable metastatic disease, likely related to the development of resistance to endocrine therapy[71]. Therefore, improving the efficacy of adjuvant endocrine therapy would be of extraordinary benefit to a large number of breast cancer patients, and is an unmet medical need.

A variety of novel agents targeting critical pathways in cellular growth and control are in development to improve the efficacy of endocrine therapy against HR+ breast cancer. Loss of control of the cell cycle, leading to unrestricted growth, is a classic hallmark of cancer[1]. Therefore, targeting cancers through the cyclin D1/CDK4/6 complex phosphorylates the retinoblastoma (pRb) protein, which leads to cell cycle activation. Results from several studies have indicated that CDK4 and CDK6 play an important role in estrogen stimulated proliferation of breast cancer cells in early to mid G1 phase[84,85,86,87,88]. Thus, CDK4 and CDK6 represent valuable therapeutic targets of HR- positive breast cancer[2].

1.2. Palbociclib Mechanism of Action

Cell cycle inhibition is a target of choice for novel cancer therapeutics. Palbociclib (PD-0332991, Ibrance®), an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK4 and CDK6 (IC_{50} = 11 nM; Ki = 2 nM) with a molecular weight of 447.53. Data from nonclinical studies indicate that palbociclib may have cytoreductive as well as cytostatic effects on tumor cells. A complete description of the activity and safety of palbociclib can be found in the Investigators Brochure[3].

The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. CDK4 and CDK6 control G1 to S phase transit by binding to D-type cyclins[4-6]. The CDK4/6/Cyclin D1 complex phosphorylates the retinoblastoma susceptibility (*RB1*) gene product (Rb), releasing the E2F and DP transcription factors that drive expression of genes required for S-phase entry[6]. CDK activity and G1 progression is negatively regulated by Cip-Kip and INK4 family, typified by p16[7-11]. Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6-associatedkinase activity and Rb phosphorylation, with subsequent cell cycle arrest[12,13].

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the cyclin D1-CDK4/6-Rb complex[14]. Cyclin D1 is a direct transcriptional target of ER[15-18] and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S-phase entry[19-23]. In addition, anti-estrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclin D1 expression[24] while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation[25]. Consistent with the notion that the main function of cyclin D1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity[26] and CDK4/6 inhibitors may be most more effective in tumors with gene amplification and overexpression of cyclin D1[27-29], which is common in ER+ breast cancer. For example, palbociclib was most effective for ER+ breast cancer in a cell line panel[30], including those that exhibited anti-estrogen resistance. Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 is particularly common in ER+ breast cancer, consistent with its critical role in the tumorigenesis of this cancer subtype[30], making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

1.3. Palbociclib Preclinical Data

Palbociclib preclinical data indicate that it may be expected to have direct effect on growth arrest as well as potential secondary cytoreductive activity. Single agent palbociclib has shown antiproliferative effects (selective G_1 arrest) on Rb-positive cancer cells *in vitro* and *in vivo*[28] where palbociclib activity was associated with reduced Rb- phosphorylation and decreased expression of the cell proliferation marker Ki67. Palbociclib showed no activity in Rb-negative tumor cell xenografts, consistent with CDK4/6 inhibition as the sole mode of action[28].

Treatment of cultured tumor cells with palbociclib causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC_{50} values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 µM, respectively. The IC_{50} values for reduction of pRb phosphorylation are similar to the IC_{50} values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to palbociclib (IC_{50} < 150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Of note for this study, ER+ breast cancer seems to be particularly appropriate for treatment with palbociclib; sensitive cell lines in this panel represent mostly the luminal ER+ subtype[30].

The combination of palbociclib with tamoxifen has been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction[30] and provided a biologic rationale for evaluating the combination of palbociclib with anti-hormonal therapy in the clinic. Also, data in hormone resistant models (MCF7-CYP19) indicate a significant benefit from the combination of palbociclib and letrozole as well as palbociclib and fulvestrant over single agent letrozole and fulvestrant[31].

The nonclinical safety profile of palbociclib has been well characterized through the conduct of single- and repeat-dose toxicity studies up to 39 weeks in duration, and safety pharmacology, genetic toxicity, reproductive and developmental toxicity, phototoxicity, and carcinogenicity studies. Consistent with the pharmacologic activity of palbociclib (cell cycle inhibition, CDK4/6 inhibition), the primary target organ findings included hematolymphopoietic (decreased cellularity of bone marrow and lymphoid organs) and male reproductive organ (seminiferous tubule degeneration, and secondary effects on the epididymis, prostate, and seminal vesicle) effects in rats and dogs, and altered glucose metabolism that was accompanied by effects on the pancreas and secondary changes in the eye, teeth, kidney, and adipose tissue in rats only, and effects on bone in rats only thatwere observed following single and/or repeat dosing at clinically relevant exposures. Altered glucose metabolism (hyperglycemia/glucosuria) correlated with pancreatic islet cell vacuolation that was determined to reflect a loss of beta cells with corresponding decreases in insulin and C-peptide. The reversibility of the effects on glucose homeostasis, pancreas, eye, kidney, and bone was not established following a 12-week non-dosing period; whereas partial to full reversal of effects on the hematolymphopoietic and male reproductive systems, teeth, and adipose tissue were observed. Additionally, a potential for QTc prolongation and hemodynamic effects were identified from safety pharmacology studies, and developmental toxicity was identified from embryo-fetal development studies in the rat and rabbit. Though gastrointestinal effects would be anticipated from a cell cycle inhibitor and while effects were observed in rats and dogs following single- and repeat-dose studies up to 3 weeks in duration (emesis, fecal changes, and microscopic changes in stomach and intestines), the effects were of limited severity at clinically relevant doses. Gastrointestinal effects were not prominent in longer duration studies, limited to effects on the glandular stomach and rodent-specific effectson the non-glandular stomach in rats following 27 weeks of intermittent dosing that did not reverse during a 12-week non-dosing period. Additional palbociclib-related findings considered non-adverse at tolerated doses based on limited severity and/or absence of degenerative changes included cellular vacuolation in multiple tissues that was morphologically consistent with phospholipidosis; hepatic (increases in liver enzymes, hepatocellular hypertrophy/increased vacuolation), renal (increased CPN), adrenal(cortical cell hypertrophy), and respiratory (clinical signs, tracheal epithelial cell atrophy)effects; and prolonged coagulation times. Reversibility (partial or full) was established for these additional toxicities. Palbociclib was determined to be an aneugen. A palbocliclib-related neoplastic microscopic finding included an increased incidence of malignant microglial cell tumors in the central nervous system of male rats at exposures higher than clinically relevant exposures. The relevance of the neoplastic finding in malerats to humans is not known, however, no cases of microglial cell tumors were reportedin humans as of the data-lock point, 02 February 2018.

1.4. Palbociclib Pharmacokinetic (PK) Data in Humans

As of 31 August 2016, twenty-seven clinical studies have evaluated the PK of palbociclib. Eight of these trials were conducted in patients with advanced malignant disease. Nineteen Phase 1 clinical pharmacology and biopharmaceutic studies of

palbociclib were conducted in healthy subjects. Eleven of these 19 clinical trials were clinical pharmacology studies conducted to investigate the absorption, distribution, metabolism, and excretion of palbociclib as well as examine the potential for drug-drug interactions (DDIs) with palbociclib. The remaining 8 of the 19 clinical trials were biopharmaceutic studies conducted to examine the bioavailability, bioequivalence, and food effect of the palbociclib formulations.

Pharmacokinetic (PK) data from patients with advanced cancer from Study A5481001 indicate that the plasma pharmacokinetics of palbociclib are low to moderately variable with generally dose proportional exposures over the dose range evaluated (25 mg to 225 mg) following single and multiple doses. PK data from Studies A5481001, A5481003, A5481010 and A541019 indicate that palbociclib is slowly absorbed with a median time of maximum concentration (T_{max}) between 4 and 8 hours post-dose, and is slowly eliminated with an elimination half-life ($t_{1/2}$) ranging from 23.2 hours to 28.8 hours. Palbociclib accumulates after repeated daily dosing (median Rac ranged from 1.9 to 2.4), which was consistent with its terminal $t_{1/2}$. In both Studies A5481010 and A5481019, the median R_{ss} (the predicted accumulation to estimate linearity) was 1.1, indicating that palbociclib clearance does not change over time. In Study A5481003, palbociclib was shown to achieve steady-state concentrations following 8 days of QD dosing. The palbociclib geometric mean volume of distribution (V_z/F) was 2583 L in patientswith advanced breast cancer (Study A5481003), which is significantly greater than total body water (42 L), indicating that palbociclib extensively distributes to peripheral tissues.

In humans, metabolism is the major route of elimination of palbociclib. Following a single oral administration of [^{14}C] palbociclib to healthy subjects (Study A5481011), the overall median recovery of the administered radioactivity in the excreta was 91.6% with a median of 17.5% recovered in urine and a median of 74.1% recovered in feces. Excretion of unchanged palbociclib in the feces and urine was 2.3% and 6.9% of dose, respectively, indicating that excretion plays a minor role in elimination of palbociclib. A study in healthy volunteers (A5481015) indicated that the absolute oral bioavailability of palbociclib was approximately 46%.

In vitro data indicate that CYP3A and sulfotransferase (SULT) enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing to steady state in humans. In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, and 2D6, and is not an inducer of CYP1A2, 2B6, 2C8, and 3A4 at clinically relevant concentrations.

In vitro evaluations indicated that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp, systemically), breast cancer resistance protein (BCRP, systemically), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, and bile salt export pump (BSEP) at clinically relevant concentrations. In vitro, palbociclib has the potential to inhibit OCT1 at clinically relevant concentrations, as well as the potential to inhibit P-gp or BCRP in the gastrointestinal tract at the proposed clinical dose. Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of palbociclib at therapeutical doses.

An itraconazole DDI study in healthy volunteers (Study A5481016) and a rifampin DDI study in healthy volunteers (Study A5481017) were conducted to evaluate the potential for strong CYP3A inhibitors and inducers, respectively, to alter the PK of palbociclib. Co-administration of itraconazole and palbociclib increased palbociclib AUC_{inf} and C_{max} by approximately 87% and 34%, respectively, relative to those when palbociclib dosewas given alone. Co-administration of rifampin and palbociclib decreased palbociclib AUC_{inf} and C_{max} by approximately 85% and 70%, respectively, relative to palbociclib given alone. Based on this data, the concurrent administration of strong CYP3A inhibitors and inducers with palbociclib should be avoided.

A midazolam DDI study in healthy volunteers (Study A5481012) was conducted to evaluate the potential for palbociclib to act as a time-dependent inhibitor of CYP3A4/5 at steady-state. Plasma midazolam C_{max} and AUC_{inf} values increased 37% and 61%, respectively, when single oral doses of midazolam were co-administered with multiple doses of palbociclib as compared to its administration alone. This is consistent with weak time-dependent CYP3A4/5 inhibition mediated by palbociclib at steady-state following daily 125 mg dosing.

PK data from the Phase 1 portion of Study A5481003 was analyzed to evaluate the potential for a drug-drug interaction (DDI) between palbociclib and letrozole at steady- state. These data indicate a lack of a potential for DDIs between palbociclib and letrozole when administered in combination.

Data from a DDI study in healthy fasted subjects in Study A5481026 indicated that palbociclib exposures were comparable when a single dose of palbociclib was co-administered with multiple doses of tamoxifen and when palbociclib was given alone.

The effect of food on the exposure of palbociclib, when administered as the commercial free base capsule, was evaluated in healthy subjects (A5481021). The study resultsindicate that palbociclib absorption and exposure were very low in approximately 13% ofthe population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Administration of palbociclib with or in between meals significantly reduced the intersubject variability (%CV). Based on these results, palbociclib commercial free base capsules should be taken with food.

The solubility of the palbociclib free base is pH dependent—palbociclib is water soluble at low pH (2.1-4.5), while the solubility dramatically decreases as pH rises above 4.5. Concomitant administration of agents which increase gastric pH can alter the solubility and absorption of palbociclib free base formulations.

In a drug interaction trial in healthy subjects (A5481038), co-administration of a single 125 mg dose of commercial free base capsule with multiple doses of the proton pump inhibitors (PPI) rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease), when compared to a single dose of palbociclib administered alone. Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-

reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists, or local antacids on palbociclib exposure. In another healthy subject study (Study A5481018), co-administration of a single dose of commercial free base capsule with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared to a single dose of palbociclib administered alone. Collectively, these antacid DDI data further support the requirement that the free base capsule of palbociclib should be taken with food.

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age range from 22 to 89 years, and body weight range from 37.9 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

Based on a population pharmacokinetic analysis that included 183 advanced cancerpatients from Studies A5481001, A5481002, and A5481003, where 40 patients had mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), and 1 patient had moderate hepatic impairment (total bilirubin >1.5 to 3.0 × ULN and any AST), indicated that there was no effect of mild hepatic impairment on the PKof palbociclib. The effect of moderate and severe hepatic impairment on the PK of palbociclib could not be evaluated as the pooled dataset included only 1 patient with moderate hepatic impairment and no patients with severe hepatic impairment.

PK analysis of the data from a separate hepatic impairment study (Study A5481013) in subjects with mild, moderate and severe hepatic impairment (as defined by Child-Pugh classification) was conducted to evaluate the impact of hepatic impairment on the PK of palbociclib. The mean fraction of unbound (f_u) palbociclib in plasma increased incrementally with worsening hepatic function. Plasma palbociclib unbound exposure ($AUC_{inf,u}$) decreased by approximately 17% in subjects with mild hepatic impairment (Child Pugh class A) and increased by approximately 34% and 77% in subjects with moderate (Child Pugh class B) and severe hepatic impairment (Child Pugh class C), respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure ($C_{max,u}$) increased by approximately 7%, 38% and 72% for mild, moderate and severe impairment, respectively, relative to subjects with normal hepatic function. Based on these data, no dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of palbociclib is 75 mg QD on Schedule 3/1.

Based on a population pharmacokinetic analysis that included 183 advanced cancerpatients from Studies A5481001, A5481002, and A5481003, where 73 patients had mild renal impairment (60 mL/min ≤ CrCl < 90 mL/min) and 29 patients had moderate renal impairment (30 mL/min ≤ CrCl < 60 mL/min), and no patients with severe renal impairment (CrCl < 30 mL/min), indicated that there was no effect of mild or moderate renal impairment on the PK of palbociclib.

PK analysis of the data from a separate renal impairment study (Study A5481014) in subjects with mild, moderate and severe renal impairment was conducted to evaluate the impact of renal impairment on the PK of palbociclib. The observed f_u in this study was consistent with the in vitro determined f_u in human plasma, and there appeared to be no obvious trend in the mean f_u with worsening renal function. Plasma palbociclib AUC_{inf} increased modestly, ranging from 31% to 42% in subjects with mild, moderate, and severe renal impairment relative to subjects with normal renal function. Plasma palbociclib C_{max}, increased by 17%, 12%, and 15% for mild, moderate, and severeimpairment, respectively, relative to subjects with normal renal function. Based on these data, no dose adjustment is required for patients with mild, moderate or severe renal impairment.

A pharmacokinetic/pharmacodynamic analysis to evaluate the relationship between palbociclib exposure and ECG variables (RR interval and QTc) was developed using data from postmenopausal women with ER-positive, HER2 negative advanced breast cancer enrolled in the QTc analysis subgroup included in Study A5481008 that was conducted as the definitive QT interval prolongation evaluation for the palbociclib program. A total of 125 patients were enrolled in this subgroup to evaluate the effect of palbociclib on the QT interval. Of these 125 patients, 77 were randomized to the palbociclib plus letrozole treatment arm and 48 were randomized to the placebo plus letrozole arm. A total of 2597 recorded individual QT intervals and 322 palbociclib concentrations obtained from 77 palbociclib plus letrozole-treated patients were included in the analysis dataset. The median (range) age and baseline body weight of patients in the analysis dataset was 62.0 (36-86) years and 72.3 (48.1-157) kg, respectively. Among the 77 patients, 70 patients provided a total of 320 matched PK-ECG pairs to evaluate the relationship between palbociclib exposure and ECG variables (RR interval and QTc). Following administration of a therapeutic regimen of 125mg palbociclib QD in combination with
2.5 mg letrozole QD, the observed plasma concentrations of palbociclib had a median (range) of 88.0 (14.7-210) ng/mL in the PK-ECG matched data. The average heart rate, RR interval, QT interval, QT interval corrected for heart rate according to Bazett (QTcB),QT interval corrected for heart rate according to Fridericia (QTcF), and QTcS (QT interval corrected for heart rate according to a study-specific correction factor) at baselinefor PK-ECG matched data were 76.0 beats per minute, 811 msec, 384 msec, 429 msec, 413 msec, and 415 msec, respectively.

The results of the analysis indicate that palbociclib does not appear to have a concentration-dependent effect on heart rate. A slight positive linear relationship betweenpalbociclib concentration and QTcS was observed; however, at the mean or median steady-state palbociclib C_{max} following administration of the recommended clinical dose of palbociclib (125 mg QD) in patients with cancer, the predicted upper bound of the one-sided 95% CI for the increase in QTcS was less than 10 msec. Palbociclib, when added toletrozole, did not prolong the QT interval to a clinically relevant extent at the recommended dosing regimen according to the criteria described in the ICH guidance for Industry E14 (ICH E14). Similar results were obtained when QTcF and QTcB were used.

An analysis to assess the relationship between palbociclib exposure and ECG endpoints (RR interval and QTc) was performed previously using pooled data from 3 clinical trials

in patients with advanced malignant disease (Studies A5481001, A5481002, and A5481003). Results from this analysis, which included data from palbociclib doses ranging from 25 mg to 225 mg QD and included a male population in addition to females, yielded the same overarching conclusion that palbociclib did not prolong the QTinterval to a clinically meaningful extent at the recommended clinical dose (125 mg QD) according to the criteria described in the ICH guidance for Industry E14 (ICH E14).

1.5. Palbociclib Clinical Data

1.5.1. Phase I Palbociclib Monotherapy Studies

Palbociclib has been tested in a Phase 1 dose escalation Study (A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment). All dose limiting toxicities (DLTs) observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. The most common non-hematological adverse events included fatigue, anemia, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. A greater proportion of patients on the 2/1 schedule had treatment emerged adverse events (TEAEs) during and after Cycle 1 than patients on the 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respectto the 2 dosing schedules, both during and after Cycle 1. One partial response (PR) was reported in a patient with testicular cancer. A total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. One of these patientswas a woman with ER+ breast cancer who had previously received 7 lines of treatment for her disease. This patient remained on treatment for 80 weeks (7 cycles at 50 mg/d and 13 cycles at 75 mg/d) and eventually discontinued treatment due to disease progression. Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, the Schedule 3/1 has been selected for further clinical development and the RP2D for this schedulewas determined to be 125 mg/day. This schedule and associated RP2D was further explored in combination with letrozole in the Phase I/II study in patients with advanced breast cancer described below.

1.5.2. Phase II palbociclib monotherapy study in advanced breast cancer

A phase II study evaluated single agent palbociclib in 37 women with advanced breast cancer[35]. Palbociclib was dosed at 125 mg orally, days 1- 21 of a 28-day cycle. The study population was 84% (HR)+/HER2-, 5% HR+/HER2+ and 11% HR-/HER2-, with a median of 2 prior cytotoxic regimens. Grade 3/4 toxicities were primarily hematologic including 51% with grade 3 neutropenia, and 51% requiring dose reduction for toxicity. Two patients experienced a PR, and 5 others had stable disease for at least 6 months, giving a clinical benefit rate of

19%, including 21% in HR+ and 29% in HR+/Her2- who had progressed through > 2 prior lines of hormonal therapy. Assessment of potential biomarkers of response, including Rb expression/localization, KI-67, p16 loss and *CCND1* amplification, did not identify a candidate tumor population. In conclusion, therapy with palbociclib monotherapy was considered well-tolerated, and demonstrates clinical benefit primarily in patients with HR+/HER2- breast cancer, including those with progression on prior hormonal- and chemotherapy.

1.5.3. Phase I/II trial of palbociclib in combination with letrozole in advanced breast cancer

A randomized, multicenter active-controlled Phase 1/2 Study (A5481003, PALOMA-1) was designed to assess the efficacy, safety and PK of letrozole 2.5 mg QD (continuously) in combination with palbociclib 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD (continuously) for the first-line treatment of ER+/ HER2- advanced breast cancer in postmenopausal women[36]. Letrozole was selected as the active control based on its worldwide approval and use as standard of care for the first-line hormonal treatment of postmenopausal women with ER+ advanced breast cancer.

Study A5481003 was comprised of a limited Phase 1 portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase 2 portion aimed at evaluating the efficacy and safety of letrozole in combination with palbociclib when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER+/HER2- advanced breast cancer. The Phase 2 portion consisted of 2 parts. In Part 1, patient selection was based only on ER/HER2 status. In Part 2, patients were prospectively selected also taking into account potential biomarkers: tumor *CCND1* amplification and/or p16 loss. A total of 177 patients were enrolled in the study. Twelve (12) were enrolled in the Phase 1 portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase 2 portion.

Results from the Phase 1 portion[37] indicated no PK interaction between palbociclib and letrozole with mean $AUC_{(0-24)}$ of 2047 and 2021 ng•hr/mL (n=12) for palbociclib in the absence and presence of letrozole, respectively, and 2027 and 1776 ng•hr/mL (n=11) for letrozole in the absence and presence of palbociclib, respectively. The RP2D was determined to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week off treatment) incombination with letrozole 2.5 mg QD continuously. PRs were reported for 3 (33%) out of 9 patients with measurable disease (3 had bone-only disease). Another 5 patients (42%) had stable disease for ≥ 6 months and the clinical benefit rate (PR + SD ≥ 6 months) was 67%.

Final results of the Phase 2 portion of the study demonstrated an improvement in the primary endpoint point of progression-free survival (PFS) for the entire study population from 10.2 months with letrozole alone, to 20.2 months with the combination of letrozole and palbociclib (Hazard Ratio 0.488, p = 0.0004), and an increase in response rate from 33% to 43%[36]. Evaluation of Cohorts 1 and 2

found improvements in both groups with the addition of palbociclib, but no apparent correlation between presence of biomarker and improved outcomes (Cohort 1, PFS 5.7 vs 26.1 mo, Hazard Ratio 0.299, p<0.0001; Cohort 2 PFS 11.1 vs 18.1 mo, Hazard Ratio 0.508, p = 0.0045). No statistically significant OS improvement in overall survival was observed in this small population (OS 33.3 months letrozole vs 37.5 months letrozole and palbociclib, Hazard Ratio 0.813, p = 0.2105).

The toxicity profile in PALOMA-1 was generally favorable and indicates that the combination of palbociclib with letrozole is well tolerated with a safety profile similar to that seen with either palbociclib or letrozole when administered alone. The most common toxicities observed with exposure to palbociclib included hematologic; 54% of patients receiving combination therapy experienced grade 3/4 neutropenia, however infectious complications, including febrile neutropenia,were not observed. Serious adverse events that occurred in more than one patient included pulmonary embolism (4%), back pain (2%), and diarrhea (2%). About 40% of patients required a delay or dose reduction due to toxicity; a total of 11 patients in the combination arm discontinued therapy due to treatment-related toxicity versus 2 in the letrozole alone arm. Other observed all-grade toxicities included nausea (26%), vomiting (14%), diarrhea (19%), and alopecia (19%). At 2 years of follow-up from this study, the cumulative incidence of neutropenia remained stable (75.8%), suggesting the hematologic toxicity of palbociclib occurs early in treatment and no data support long-term or cumulative hematologic toxicity after exposure to palbociclib.

Multiple trials are ongoing in advanced breast cancer to better define the role of palbociclib in metastatic ER+/HER2- disease. This includes two global randomized Phase 3 studies have completed enrollment and are still ongoing: Study A5481008, a study of letrozole +/- palbociclib in front-line advancedbreast cancer (ABC) and Study A5481023, a study of fulvestrant +/- palbociclib in recurrent ABC.

In February 2015, based on the published data in PALOMA-1, the Food and Drug Administration granted accelerated approval to palbociclib, to be used in combination with letrozole for initial endocrine-based therapy for metastaticbreast cancer in postmenopausal women with ER+/HER2- advanced breast cancer.

1.6. Clinical Safety Overview for Palbociclib

The overall safety profile of palbociclib is based on pooled data from 872 patients who received palbociclib in combination with endocrine therapy (N=527 in combination with letrozole; N=345 in combination with fulvestrant) in 3 randomized clinical trials in HR-positive, HER2-negative advanced or metastatic breast cancer. Table 1 presents adverse drug reactions of any grade reported in these 3 clinical trials. The most common AEs were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, and diarrhea. The most common (≥ 2%) Grade ≥ 3 AEs were neutropenia, leukopenia,

anemia, fatigue, and infections. Dose reductions or dose modifications due to any AEs occurred in 34.4% of patients regardless of the combination. Permanent treatment discontinuation associated with AEs as occurred in 4.1% of patients.

Table 1. Adverse Drug Reactions From 3 Randomized Studies in Patients With HR Positive, HER2 Negative Advanced or Metastatic Breast Cancer (N=872)

System Organ Class **Frequency** **Preferred Term**[a]	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Infections and infestations			
Very common			
Infections[b]	523 (60.0)	53 (6.1)	9 (1.0)
Blood and lymphatic system disorders			
Very common			
Neutropenia[c]	719 (82.5)	499 (57.2)	101 (11.6)
Leukopenia[d]	430 (49.3)	260 (29.8)	8 (0.9)
Anemia[e]	261 (29.9)	48 (5.5)	2 (0.2)
Thrombocytopenia[f]	197 (22.6)	17 (2.0)	4 (0.5)
Common			
Febrile neutropenia	13 (1.5)	11 (1.3)	2 (0.2)
Metabolism and nutrition disorders			
Very common			
Decreased appetite	160 (18.3)	8 (0.9)	0 (0.0)
Nervous system disorders			
Common			
Dysgeusia	81 (9.3)	0 (0.0)	0 (0.0)
Eye disorders			
Common			
Vision blurred	49 (5.6)	1 (0.1)	0 (0.0)
Lacrimation increased	62 (7.1)	1 (0.1)	0 (0.0)
Dry eye	39 (4.5)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders			
Common			
Epistaxis	77 (8.8)	0 (0.0)	0 (0.0)
ILD/pneumonitis[i] (identified post-marketing)[i]	12 (1.4)	1 (0.1)	0 (0.0)
Gastrointestinal disorders			
Very common			
Stomatitis[g]	269 (30.8)	8 (0.9)	0 (0.0)
Nausea	317 (36.4)	5 (0.6)	0 (0.0)
Diarrhoea	243 (27.9)	10 (1.1)	0 (0.0)
Vomiting	167 (19.2)	6 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders			
Very common			
Rash[h]	164 (18.8)	8 (0.9)	0 (0.0)
Alopecia	235 (27.0)	0 (0.0)	0 (0.0)
Dry skin	96 (11.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Very common			
Fatigue	366 (42.0)	26 (3.0)	2 (0.2)
Asthenia	120 (13.8)	14 (1.6)	0 (0.0)

Table 1. Adverse Drug Reactions From 3 Randomized Studies in Patients With HR Positive, HER2 Negative Advanced or Metastatic Breast Cancer (N=872)

System Organ Class **Frequency** **Preferred Term**[a]	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Pyrexia	121 (13.9)	1 (0.1)	0 (0.0)
Investigations *Very common* Alanine aminotransferase increased Aspartate aminotransferase Increased	 96 (11.0) 104 (11.9)	 18 (2.1) 22 (2.5)	 2 (0.2) 0 (0.0)

N/n=number of patients

a. Preferred terms (PTs) are listed according to Medical Dictionary for Regulatory Activities (MedDRA) 19.0, unless otherwise noted.
b. INFECTIONS includes all PTs that are part of the System Organ Class Infections and infestations.
c. NEUTROPENIA includes the following PTs: Neutropenia, Neutrophil count decreased.
d. LEUKOPENIA includes the following PTs: Leukopenia, White blood cell count decreased.
e. ANEMIA includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.
f. THROMBOCYTOPENIA includes the following PTs: Thrombocytopenia, Platelet count decreased.
g. STOMATITIS includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
h. RASH includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.
i ILD/pneumonitis includes any reported PTs that are part of the Standardised MedDRA Query Interstitial lung disease (narrow).

The adverse drug reaction table (Table 1) includes data from the studies A5481003, A5481008 and A5481023 with cut-off date 15 November 2018..

Overall, neutropenia of any grade was reported in 719 (82.5%) patients regardless of the endocrine therapy combination, with 499 (57.2 %) being Grade 3 and 101 (11.6%) being Grade 4 (Table). Eleven (1.3%) patients permanently discontinued due to neutropenia. 13(1.5%) patients experience febrile neutropenia, of which 11 (1.3 %) were Grade 3 and 2 (0.2%) was Grade 4.

1.7. Palbociclib and Endocrine Therapy Pharmacokinetics

Results from the Phase 1 portion of PALOMA-1 indicated no PK interaction between palbociclib and letrozole with mean AUC (0-24) of 2002 and 2043 ng•hr/mL (n=11) for palbociclib in the absence and presence of letrozole.

The potential for a DDI between palbociclib and tamoxifen is considered to be probable based on in vitro data. Multiple enzymes are responsible for the metabolism of tamoxifen and its active metabolites including CYP3A4, CYP2C9, and CYP2D6. In vitro evidence suggest that tamoxifen and one of its primary active metabolites, 4-hydroxy-tamoxifen, are inducers of CYP3A4 enzymes. In clinical trials, co-administration of tamoxifen with letrozole and anastrozole (both CYP3A4 substrates) has resulted in decreased exposures (AUC) of each by 37% and 27%, respectively. Palbociclib is a CYP3A4 substrate and CYP3A4 is thought to be the primary route of the oxidative metabolism of palbociclib.

Thus, the co-administration of tamoxifen and palbociclib may lead to lower circulating levels of palbociclib and require an upward dose adjustment in palbociclib if these two compounds are used in conjunction. Additionally, time-dependent inhibition of CYP3A4 has been observed in preclinical studies of palbociclib.

The effect of multiple dosing of tamoxifen (60 mg QD for 4 days followed by 20 mg QD for 23 days), on the single-dose PK of palbociclib (125 mg), was evaluated in 25 healthy fasted subjects in Study A5481026. Administration of palbociclib in the presence of tamoxifen and its metabolites (4-hydroxy-tamoxifen, N-desmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen) at steady state showed that palbociclib exposure was comparable with that when palbociclib was given alone. The ratios (90% CIs) of the adjusted geometric means of palbociclib AUC_{inf} and C_{max} were 108% (104%-111%) and 116% (105%-129%), respectively, following administration of palbociclib with multiple doses of tamoxifen (Test) relative to palbociclib administered alone. These results indicate that it is not necessary to adjust palbociclib starting dose when co-administering with tamoxifen[3]. A two-way DDI assessment between palbociclib and tamoxifen incancer patients has been incorporated into the ongoing PENELOPE[B] Study[92,93].

The potential for a clinically significant DDI between palbociclib and anastrozole is considered to be low. Anastrozole inhibited CYP1A2, 2C8, 2C9, and 3A4 in vitro with Ki values ~30-fold higher than the steady-state C_{max} values observed following a 1mg daily dose. In vitro and in vivo assessments of oxidative metabolism have indicated the route of formation of the primary metabolite hydroxyanastrozole is predominantly through CYP3A4. Time dependent inhibition of CYP3A4 has been observed in in vitro studies of palbociclib, thus palbociclib has the potential to inhibit the primary clearance pathway of anastrozole. A two-way DDI assessment between palbociclib and anastrozole has been incorporated into the ongoing PENELOPE[B] Study [92].

The potential for a clinically significant DDI between palbociclib and exemestane is considered to be very low. Exemestane is metabolized by cytochrome P 450 3A4 (CYP 3A4) and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1, and 3A4. Therefore, exemestane is unlikely to affect palbociclib PK. Rifampin reduced exemestane exposure by ~50%. However, in a clinical pharmacokinetic study, co-administration of ketoconazole, a potent inhibitor of CYP 3A4, had no significant effect on exemestane pharmacokinetics. Therefore, it is unlikely that palbociclib, which is a weak time-dependent inhibitor of CYP34, will have an effect on exemestane PK. A two-way DDI assessment between palbociclib and exemestane has been incorporated into the ongoing PEARL Study[92, 93]. An interim analysis of the PK datafrom the PEARL Study indicated there is no clinically relevant DDI between palbociclib and exemestane when the 2 drugs are coadministered[97].

The potential for a clinically significant DDI between palbociclib and goserelin is considered to be very low. Goserelin is a synthetic decapeptide analogue of gonadotropin releasing hormone (GnRH) whose primary route of elimination is the cleavage of C-terminal amino acids followed by renal excretion. No formal drug-drug interaction studies have been performed and no confirmed interactions have been reported between

goserelin and other drugs. A DDI assessment between palbociclib and goserelin has been included into two ongoing studies; A5481023 and the PENELOPE[B] Study.

1.8. Study Rationale

Although many patients with HR+/HER2- breast cancer may be cured of their disease with optimal local and systemic therapy, a significant number of patients with stage II and III disease will experience disease recurrence. Adjuvant endocrine therapy for breast cancer can be extremely effective, particularly with extension beyond 5 years, however disease recurrence can occur, with risk distributed over the decades following initial diagnosis. Methods to improve the efficacy of endocrine therapy, and delay the onset of resistance, are needed.

HR+ breast cancer biologically may demonstrate features suggestive of sensitivity to CDK4/6 inhibition with agents such as palbociclib. Given the demonstrated activity and safety of palbociclib in the first-line treatment of metastatic HR+/ HER2- breast cancer, supporting FDA approval, there is interest in whether the benefits of CDK4/6 inhibition may translate into the adjuvant setting. The purpose of the PALLAS study is to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR+/HER2- early breast cancer. Assessment of avariety of correlative analysis, including evaluation of the effect of palbociclib in genomically defined tumor subgroups, is planned.

Complete information for palbociclib (PD-0332991 or Ibrance®) may be found in the Single Reference Safety Document for the compound, which for this study is the applicable current version of the Investigator's Brochure of palbociclib. The Single Reference Safety Document for the active comparator agents, letrozole, anastrozole,exemestane, tamoxifen and LHRH agonists will be the publicly available US Package inserts, or local equivalent depending on country-specific regulations.

1.8.1. Rationale for the Duration of Palbociclib Treatment

The specific elements of the rationale for evaluation of 2 years of treatment with palbociclib in the adjuvant treatment setting are outlined in detail throughout Section 1. These include risk of recurrence in the proposed population, mechanism of action of the drug, potential synergistic effects when given with hormonal therapy, information to date about the pattern of hematologic effects over time, and specific elements put in place to ensure optimal monitoring and iterative assessment of the safety profile.

Given that the annual odds of the risk of disease recurrence in HR positive, HER2 negative EBC are consistent and distributed quite evenly up to >20 years from the initial diagnosis, extending the length of endocrine therapy has been proven to be associated with increased benefits[38,39]. Similar to an anti-estrogen agent, palbociclib inhibits the proliferation of ER-positive breast cancer but is notknown to cause apoptosis or cell death.

While senescence is an appealing mechanism of cell demise and is indeed observed in vitro after exposure of breast cancer cells and tumors to a combination of endocrine therapy and palbociclib[89], the data in human trials are lacking about the degree of cell demise caused by combined palbociclib and anti-ER treatment. Moreover, in vitro data showed that, after removing palbociclib and/or the anti-ER agent, the cells can eventually re- start to divide[90]. Considering the synergistic mechanism of action with anti-hormonal agents and synergistic signaling through the same CDK4/6 dependent mechanism, it is likely that the anti-proliferative mechanism of action will require longer treatment for optimal antitumor effect. The benefit of increasing the length of treatment was clearly demonstrated for anti-hormonal agents when years of testing taught us that an enhanced benefit of tamoxifen in patients with EBC could be achieved by extending the length of therapy. Increased benefit with extending the length of therapy has also been demonstrated for other anticancer agents in other tumors (e.g. Gleevec® in gastrointestinal stromal tumor and chronic myelogenous leukemia). Thus, as predicted mechanistically, it is hypothesized that the longer a patient receives combined treatment with palbociclib and an antiestrogen, the more likely they may receive prolonged clinical benefit.

It is therefore proposed to administer palbociclib for 2 years under close monitoring of emerging safety data both before PALLAS start and during the clinical trial.

1.8.2. Rationale for the Collection of Tissue and Blood Samples

The preclinical data cited above suggested specific tumor alterations as predictors of response based upon palbociclib's mechanism of action. However, analyses of cell cycle biomarkers in the PALOMA-1 study and others did not identify a predictive marker beyond estrogen receptor (ER) [91]. While ER is a strong positive predictor of response, not all ER+ patients will initially respond to the combination of endocrine therapy and palbociclib, and in others, resistance will emerge. Furthermore, no prospective evaluation of the predictive capacity of ER receptor as a biomarker is available in humans, and the limited number of patients with ER- disease treated with palbociclib precludes comparative analysis. Within the cohort of patients with ER + disease, ongoing efforts are needed to identify tumors and patients that will derive the greatest benefit from CDK4/6 inhibition, particularly in the curative setting. A robust biospecimen bank is essential to accomplishing this task; primary tumor tissue collection will be mandatory for all patients enrolled on the PALLAS trial. The resulting tumor bank will provide an invaluable resource to evaluate a large range of potential biomarkers, both through pre-specified analyses and exploratory investigations. Molecular analyses of breast cancer, pioneered by Perou and colleagues in 2000, have identified different subtypes of this disease, such as Luminal A, Luminal B, basal-like, HER2 type, etc.[40]. Each subtype of breast cancer has its distinct molecular features, and the disease prognosis for each subtype is different. In addition to clinical parameters, such as tumor size, grade, and node status, subtyping breast cancer may help in decisions about treatment options.

The preclinical development of palbociclib, demonstrated the greatest sensitivity (as evidenced by the lowest IC50) to palbociclib in tumors of the luminal subtype[94].

In PALLAS, molecular tests will be applied to the tumor samples from allpatients enrolled in the study. This test will be performed retrospectively, and a prospectively defined analysis will be conducted to assess the response to palbociclib plus endocrine therapy in Luminal A and Luminal B patients and in the non-luminal subtype (further details in SAP).

ER targeting and estrogen signaling blocking therapies, such as tamoxifen and AIs, have been proven to be effective treatments for ER-positive breast cancer. However, de novo and acquired resistance to anti-hormonal therapies may occur. Possible mechanisms of resistance include the presence of variant ER, ER mutations, the absence or loss of ER and altered expression of receptor- interacting proteins[42,43]. Those tumor features will be evaluated in PALLAS specimens as well as other potential factors influencing benefits of adding a CDK4/6 inhibitor to standard endocrine therapy. Furthermore, collection of serum samples serially during PALLAS follow up will provide the opportunity to examine developing processes of tumor resistance and emergence from tumor dormancy.

Additional planned analysis to identify predictors of therapeutic benefit by adding palbociclib to endocrine therapy include candidate gene approaches, such as examining genes, proteins, and RNAs relevant to cell cycle (e.g., *CCND1* amplification, *CDKN2A* loss), drug target (CDK4/6), and tumor sensitivity and/or resistance (Ki67, pRb, cyclin E, etc.). Global gene profiling such as whole exome sequencing may be applied to a subset of samples in this study, if patient tumor volume of samples allow. Planning and execution of these translational studies are overseen by the TRANS-PALLAS subcommittee. For details of translational analysis please refer to translational sub protocols and translational statistical analysis plan.

1.8.3. Rationale for Patient Reported Outcome (PRO) Assessments

Patient Reported Outcomes Questionnaires should be incorporated in order to evaluate the impact of adjuvant endocrine therapy with or without palbociclib on the quality of life (QOL) of HR+/HER2- breast cancer patients and provide a comprehensive risk benefit assessment that includes the patient perspective in addition to efficacy and safety. The questionnaires can evaluate the impact of treatment and related side effects on symptoms, functioning and global QOL. In addition to known side effects of tamoxifen therapy (e.g. hot flushes, weight gain, vaginal bleeding), AIs have a different toxicity profile with side effects, such as arthralgia, myalgia, joint pain, bone loss, cognitive dysfunction, increased risks of rash, nausea, diarrhea and vomiting. AIs, however, have been shown to have less vaginal bleeding and thromboembolic complication (i.e., 71%decreased risk of vaginal bleeding and 47% decreased risk of thromboembolic

events) than tamoxifen[67,68]. In addition, results of the ATAC study showed that patients treated with AIs have more symptoms of vaginal dryness, pain on intercourse and loss of sexual interest than patients receiving tamoxifen therapy. During that trial, some endocrine related symptoms (hot flushes, night sweats, gynaecological and sexual symptoms) improved during the study period, while other symptoms (reduced libido and vaginal dryness) persisted[68,69]. Similarly, patients treated with AI (letrozole) in the MA.17 study showed significant differences in night sweats, aching in muscles and joints, difficulty sleeping and vaginal dryness compared to the placebo group. Those patients had worse bodily pain domain scores assessed with the SF-36 and more vasomotor symptoms as assessed with the MENQOL instrument[70].

Application of targeted drugs (e.g., palbociclib) in the therapy of breast cancer has showed significant clinical benefit, but may introduce new side effects. In the Phase I/II trial (A5481003) of palbociclib in combination with letrozole in ER+/HER2-negative advanced breast cancer in postmenopausal women, the most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, fatigue, nausea, hot flush, alopecia, arthralgia, diarrhea, decreased appetite, headache, dyspnea, asthenia, vomiting and cough[36]. The significance of these symptoms and impact on patient functioning and global QOL will be evaluated in PALLAS study.

1.8.4. Benefit-Risk Assessment

As described above, HR+ breast cancer is the most commonly diagnosed subset of breast cancer, and affects thousands of patients every year. Despite the efficacy of up to 10 years of adjuvant endocrine therapy, a percentage of patients will relapse with incurable metastatic disease, with risk extending for many yearsafter initial diagnosis. Therefore, improving the efficacy of adjuvant endocrine therapy would be of extraordinary benefit to a large number of breast cancer patients, and is an unmet medical need.

Data from PALOMA-1 has demonstrated a significant prolongation of median progression-free survival with the combination of palbociclib and letrozole compared with letrozole alone. The toxicity profile of palbociclib at the dose and schedule similar to the one that will be used in the PALLAS study was moderate, with neutropenia being the most frequent treatment related adverse event. The clinical picture of neutropenia seen with the palbociclib/letrozole combination in PALOMA-1 is notable for being quickly reversible, noncumulative and uncomplicated and managed without the use of growth stimulating factors. The data generated from PALOMA-1 has supported accelerated approval by FDA in the US of palbociclib in combination with letrozole for advanced HR+/HER2- breast cancer.

In the PALLAS trial, all study participants are expected to have undergone adequate initial local treatment for their breast cancer including surgical resection, with or without adjuvant radiotherapy. For details, please refer to

Appendix D. Participants are also expected to have selected an appropriate systemic therapy plan, with or without chemotherapy and have decided to receive endocrine therapy. All patients, regardless of randomization arm, will receive standard adjuvant endocrine treatment according to institutional standards. It is not expected that toxicity of palbociclib will reduce compliance with endocrine treatment.

As described before, there are no obvious differences in the clinical and laboratory safety profile between patients taking palbociclib for less than 12 months compared to those taking the drug for 12 months or longer based on data collected in clinical studies to date. It is concluded that the data available do not identify any safety concerns associated with long term administration of palbociclib. Given the increasing use of longer duration endocrine therapy andthe known prolongation of cancer recurrence risk well beyond 5 years, palbociclib therefore will be administered for 2 years.

In addition, participating patients in the current trial will have marginal additional burden due to investigations required for study participation (e.g. additional visits at the site, additional blood tests, and completion of questionnaires). However, the option to receive a treatment potentially significantly improving iDFS in this population is considered to balance uncertainties of the toxicity profile of palbociclib and the additional burden related to study investigations.

2. Objectives

2.1. Primary Objective

To compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment versus at least 5 years endocrine therapy alone in patients with histologically confirmed HR+/HER2- invasive early breast cancer (EBC).

2.2. Secondary Objectives

(1) To compare the following endpoints: iDFS excluding second primary invasive cancers of non-breast origin, distant recurrence-free survival (DRFS), locoregional recurrences-free survival (LRRFS), and overall survival (OS).

(2) To compare the safety of 2 years of palbociclib with adjuvant endocrine therapy versus adjuvant endocrine therapy alone.

2.3. Translational Science Principal Objective

(1) To compare baseline tumor tissue to determine whether there is prognostic or predictive utility for defined genomic subtypes (luminal A, luminal B and non- luminal) with respect to iDFS and OS.

2.4. Translational Science Additional Objectives

(1) To evaluate iDFS and OS in other genomically-defined breast cancer prognostic, theranostic, or predicted subgroups based on pre-specified genomic assays

(2) To evaluate baseline tumor- and blood-based markers as predictors of benefit from the addition of palbociclib to endocrine therapy.

(3) To evaluate tumor- and blood-based markers at time of disease recurrence for mechanisms of resistance to palbociclib and endocrine therapy.

(4) To perform exploratory analyses of serum and plasma samples over time to investigate the predictive and prognostic value of novel biomarkers in this specific trial setting related to efficacy or safety of the agent.

(5) To compare serial levels of circulating cell-free DNA (cfDNA) in patients receiving palbociclib and endocrine therapy versus endocrine therapy alone.

(6) To evaluate pharmacogenomic and pharmacogenetic predictors of toxicity and efficacy of palbociclib and endocrine therapy and to endocrine therapy alone.

2.5. Clinical Science Objectives

(1) To evaluate adherence to oral therapy in patients receiving palbociclib and endocrine therapy.

(2) To determine the association of BMI with the efficacy of palbociclib and endocrine therapy.

2.6. Patient-Reported Outcomes Objective

(1) To compare patient-reported quality of life, fatigue, arthralgia, alopecia, menstrual function, and endocrine symptoms of HR+/HER2- breast cancer patients randomized to receive palbociclib plus adjuvant standard endocrine therapy versus standard endocrine therapy alone overall and by subgroups defined by age at randomization (≤50 and >50) and initial endocrine therapy (tamoxifen and AI) at multiple pre-specified time points.

2.7. Endpoints

2.7.1. Primary Endpoint

(1) Invasive disease-free survival (iDFS) defined according to STEEP criteria.

2.7.2. Secondary Endpoints

(1) Invasive disease-free survival (iDFS) excluding second primary invasive cancers of non-breast origin as an event.
(2) Overall Survival (OS)
(3) Locoregional recurrences-free survival (LRRFS) defined as the composite of local/regional ipsilateral recurrence, contralateral invasive breast cancer or death from any cause
(4) Distant recurrence free survival (DRFS) is defined according to STEEP criteria as the composite of distant recurrence or death from any cause.
(5) Adverse Events

2.7.3. Clinical Science Endpoints

(1) Adherence measured by Drug Diary, Morisky Medication Adherence Scale, Medication Adherence and McHorney Brief Estimator questionnaires in a subset of patients.
(2) Primary endpoint (iDFS) effected by baseline body mass index (BMI).

2.7.4. Patient-Reported Outcomes Endpoint

(1) Actual Scores and Change from baseline in functioning, symptoms, and global QOL

2.7.5. Translational Science Principal Endpoint

(1) Biomarker(s) reflective of or associated with breast cancer luminal subtypes

3. Study Design

3.1. Overall Description of Study Design

This is a two-arm, randomized, open label, Phase III, multicenter study to evaluate the effect on iDFS of combining at least 5 years of adjuvant standard endocrine therapy and 2-year adjuvant palbociclib treatment (Arm A) versus at least 5 years of adjuvant standard endocrine therapy alone (Arm B) in pre-and postmenopausal women and men with HR+ / HER2-, Stage II or III (Stage IIA limited to 1000 patients) early invasive breast cancer patients.

PALLAS SCHEMA

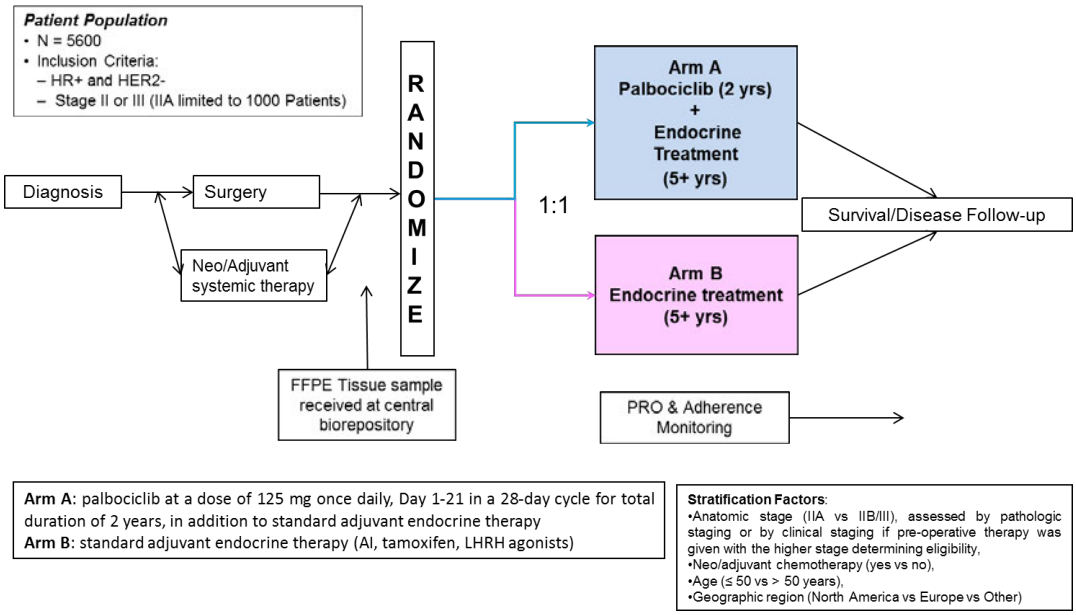

Figure 1: *PALLAS Study Schema*

Endocrine adjuvant therapy may have started before randomization and be ongoing at that time.

Approximately 5600 patients (revised target accrual) from approximately 500 global sites will be randomized into one of the two treatment arms with a 1:1 randomization ratio.The dosing schedule for both Arms, and potential dose reduction strategies, are given in section 9:

Arm A: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years (refer to 6.1.2 for details), in addition to standard adjuvant endocrine therapy for a duration of at least 5 years.

Arm B: standard adjuvant endocrine therapy for a duration of at least 5 years

Standard endocrine therapy (also referred to as background treatment) can be tamoxifen or aromatase inhibitor with or without LHRH agonist.

In order to participate in the trial, a patient must fulfill all inclusion criteria and must not meet any of the exclusion criteria. Furthermore, a patient will need to consent for study participation and to the collection storage and analysis of his/her blood and tumor tissue samples for biomarker research as specified in section 14. Prior to randomization, a

representative tumor tissue block must be made available to the central sample repository.

4. Patient Selection

4.1. Inclusion Criteria

Please note that waivers to eligibility requirements are not allowed.

Patients must meet the following criteria for study entry:

4.1.1. Patient/Disease Specifics

(1) Signed informed consent obtained prior to any study specific assessments and procedures.

(2) Age ≥18 years (or per national guidelines).

(3) Premenopausal and postmenopausal women or men with Stage II (Stage IIA limited to a maximum of 1000 patients) or Stage III early invasive breast cancer per AJCC (American Joint Committee on Cancer) Breast Cancer Staging version 7 / UICC (Union for International Cancer Control)[54]. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT, is at the discretion of the investigator.

If neoadjuvant systemic therapy was received (either chemotherapy or endocrine therapy or biologic therapy excluding 'Anti-HER2 treatment'), either initial clinical stage (determined by physical and/or radiologic examination) or post-operative pathologic stage can be used foreligibility purposes, with the higher stage determining eligibility.

(4) Patients with multicentric and/or multifocal and/or bilateral early invasive breast cancer whose histopathologically examined tumors all meet pathologic criteria for ER+ and/or PR+ and HER2-.

(5) Patients must have histologically confirmed hormone receptor positive (ER+ and/or PR+), HER2-, early invasive breast cancer. ER, PR and HER2 measurements should be performed according to institutional guidelines, in a CLIA-approved setting in the US or certified laboratories for Non-US regions. Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines[55, 95]. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment. Testing may occur on diagnostic core or surgical tumor tissue.

(6) Patients must have undergone adequate (definitive) breast surgery for the current malignancy. For details please refer to Appendix D.

(7) A formalin-fixed paraffin-embedded (FFPE) tumor tissue block must be

transmitted to a central sample repository and confirmation of receipt must be available prior to randomization. For details please refer to section 8.2.

(8) ECOG performance status 0-1.

(9) Patients must be able and willing to swallow and retain oral medication without a condition that would interfere with enteric absorption.

(10) Serum or urine pregnancy test must be negative within 7 days of randomization, in women of childbearing potential. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. Women of childbearing potential and male patients randomized into treatment Arm A or B must use adequate contraception for the duration of protocol treatment and for 6 months after the last treatment with palbociclib if they are in arm A. In addition, patients receiving standard adjuvant endocrine therapy (Arm A and Arm B) should use adequate contraception in accordance with the specific medication requirements (e.g. Summary of Product Characteristics). Adequate contraception is defined as one highly effective form (i.e. abstinence*, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusive cap with spermicidal foam / gel / film / cream / suppository).

*Abstinence is to be interpreted as “true abstinence” for heterosexual intercourse and therefore, “periodic abstinence” (e.g. calendar, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not considered highly effective.

4.1.2. Prior Treatment Specifics

(11) Patients may or may not have received neo/adjuvant therapy, but must be after last dose of chemotherapy and/or biologic therapy and must have sufficientresolution of side effects per physician assessment at the time of randomization.

(12) Patients may or may not have received breast/axilla/ post-mastectomy chest wall radiotherapy, but must be after last dose of radiotherapy and must have sufficient resolution of side effects per physician assessment at the time of randomization.

(13) Patients must have sufficient resolution of any surgical side effects from the last surgery per physician assessment, with no active wound healing complications at the time of randomization.

(14) Patients must either be initiating or have already started **adjuvant hormonal treatment**. Patients may already have initiated endocrine therapy at the time of randomization, but randomization must take place within 12 months of date of histological diagnosis and within 6 months of initiating standard adjuvant endocrine therapy. Patients who received **neoadjuvant endocrine therapy** are eligible as long as they are randomized within 12 months of initial histological diagnosis and after completing no more than 6 months of adjuvant endocrine therapy. Patients may be receiving either tamoxifen or aromatase inhibitor (AI: letrozole, anastrozole, or exemestane). For premenopausal patients and men, concurrent LHRH agonist use is allowable and may also be ongoing at the time

of randomization. If a LHRH agonist was used for ovarian protection during neo/adjuvant chemotherapy it is allowable and shall not be taken into account for calculations regarding the 6 months standard adjuvant endocrine therapy.

4.1.3. Baseline Body Function Specifics

(15) Absolute neutrophil count ≥ 1,500/mm^3.
(16) Platelets ≥ 100,000/mm^3.
(17) Hemoglobin ≥ 10g/dL.
(18) Total serum bilirubin ≤ ULN; or total bilirubin ≤ 3.0 × ULN with direct bilirubin within normal range in patients with documented Gilbert's Syndrome.
(19) Aspartate amino transferase (AST or SGOT) and alanine amino transferase (ALT or SGPT) ≤ 1.5 × institutional ULN.
(20) Serum creatinine below the upper limit of the institutional normal range (ULN) or creatinine clearance (or glomerular filtration rate [GFR]) ≥ 60 mL/min/1.73 m^2 for patients with serum creatinine levels above institutional ULN.

4.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

(1) Concurrent therapy with other Investigational Products.
(2) Prior therapy with any CDK inhibitor.
(3) Patients with Stage I or IV breast cancer are not eligible. Baseline staging to document absence of metastatic disease is not required, however is recommended as determined by institutional practice (in patients where there may be a reasonable suspicion of advanced disease e.g., large tumors, clinically positive axillary lymph nodes, signs and symptoms). If performed, reports of these examinations must be available. Examination type for staging, i.e. X-ray, sonography, bone scan, CT, MRI, and/or PET-CT, is at the discretion of the investigator.
(4) History of allergic reactions attributed to compounds of chemical or biologic composition similar to palbociclib.
(5) Patients receiving any medications or substances that are potent inhibitors or inducers of CYP3A isoenzymes within 7 days of randomization (see Section 9.5.2.1 for list of CYP3A inhibitors and inducers).
(6) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, diabetes, or psychiatric illness/social situations that would limit compliance with study requirements. Ability to comply with study requirements is to be assessed by each investigator at the time of screening for study participation.
(7) Pregnant women, or women of childbearing potential without a negative pregnancy test (serum or urine) within 7 days prior to randomization, irrespective of the method of contraception used, are excluded from this study because the effect of palbociclib on a developing fetus is unknown. Breastfeeding must be discontinued prior to study entry.

(8) Patients with a history of any malignancy are ineligible except for the following circumstances:

- Patients with a malignancy history other than invasive breast cancer are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy.
- Patients with the following cancers are eligible, even if diagnosed andtreated within the past 5 years: ductal carcinoma *in situ* of the breast,cervical cancer *in situ*, and non-metastatic non-melanomatous skin cancers.

(9) Patients are not eligible if they have previously received endocrine therapy within 5 years prior to diagnosis of the current malignancy. This includes use for prophylactic reasons, including treatment of osteoporosis or cancer prevention with tamoxifen, raloxifene or AI. Patients may concurrently receive bisphosphonates or rank ligand inhibitors while on this study if necessary for treatment or prevention of osteopenia or osteoporosis.

(10) Patients on antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions or increased immunosuppression with palbociclib.

(11) Patients with clinically significant history of chronic liver disease, including chronic/active viral or other known hepatitis, current alcohol abuse, or cirrhosis, etc.

(12) Patients receiving concurrent exogenous hormone therapy (hormone replacement therapy, oral or any other hormonal contraceptives such as hormonal contraceptive coil, etc.) are not eligible but topical vaginal estrogen therapy is allowable.

5. Method of Treatment Assignment/Patient Randomization

5.1. Site Enrollment Requirements

Following regulatory and ethical approval for each participating site, it is the responsibilities of the respective Sponsor (AFT for US sites, ABCSG for non-US sites) to formally activate sites according to local obligations. Sites will only be able to enroll patients once formal site activation has been performed by the Sponsor.

5.2. Patient Randomization Procedure

After written informed consent has been obtained, the study site will obtain a unique patient number or unique patient identifier which will stay the same throughout the entire study covering all study periods (as described in section 6.1.) via an interactive voice and/or web-based response system (IxRS). At this time point the patient is *enrolled* into the study.

Once eligibility has been established and the patient specific tumor block has been confirmed as received at the central sample repository, the patient may be *randomized*, and the site will obtain the patient's treatment assignment (Arm A or Arm B) from the IxRS. As this is an open label trial, treatment assignments will not be blinded. Patients enrolled but not randomized for any reason have to be registered as Screening Failure in IxRS.

5.3. Stratification Factors

Patients will be randomized into one of the treatment arms in a 1:1 ratio.
Stratification factors used at time of randomization include:

- Anatomic stage (IIA vs IIB/III), assessed by pathologic staging or by clinical staging if pre-operative therapy was given with the higher stage determining eligibility,
- Neo/adjuvant chemotherapy (yes vs no),
- Age (≤ 50 vs > 50 years),
- Geographic region (North America vs Europe vs Other)

6. Study Assessments and Procedures

6.1. Study Phases

The study consists of 4 different phases which apply to both of Arms A and B:

- Screening Phase
- Treatment Phase
- Follow-Up Phase I
- Follow-Up Phase II

See Appendix B for details as to how these phases correspond with the Schedule of Assessments calendar, Screening Phase, Treatment Phase and Follow-Up Phases I and II (please also refer to Sections 7, 9, and 10).

6.1.1. Screening Phase

The Screening Phase is the time between the date a patient provides written informed consent, and the time the patient completes randomization. Data collection and procedures during this time period include patient demographics, eligibility requirements, concomitant medications, type of endocrine therapy, medical history, physical examination/vital signs, ECOG performance status assessment, laboratory measurements, pregnancy testing (if applicable), biospecimens (blood and tissue samples), and PRO assessments (see sections 7). During the Screening Phase, only AEs deemed to be serious (SAEs) and related to protocol mandated and not routinely performed procedures have to be reported.

During the Screening Phase, all laboratory assessments must be performed within 14 days of randomization. If screening assessments occur within 7 days before Cycle 1 Day 1, then they may serve as the Cycle 1 Day 1 assessments also and do not need to be repeated.

Male patients should be specifically informed about the fact that the effect of palbociclib on sperm production is not entirely clear. Therefore it is recommended for men who want to have children at a later time, to consider

sperm preservation prior to beginning therpay with palbociclib. Additionally men should not donate semen or father a child within treatment phase and 6 months thereafter.

6.1.2. Treatment Phase

During this phase, patients randomized into Arm A will receive IP treatment (palbociclib) and Non-IP treatment and patients randomized into Arm B will receive Non-IP treatment only (standard endocrine therapy).
Treatment Phase for patients on both Arms can start at the day of randomization if both IP and Non-IP treatment are initiated on that day. However, patients will have the opportunity to start treatment within 7 days from randomization. For patients on Arm B, who have already started Non-IP treatment prior to randomization (maximum of 6 months adjuvant endocrine therapy) the date of randomization will be considered as start of the Treatment Phase as well as Cycle 1 Day 1.

As the intention is to administer at least 5 years of endocrine therapy alone (Arm B), or with 2 years of concurrent palbociclib (Arm A), 2 years will be used as the time period for this phase. IP treatment is to be given for 2 years, which is a total of twenty-six 28-days cycles (for patients without interruptions or delays) and the goal is not to administer a specific number of cycles, but to allow for completion of a cycle if it has started prior to two years from randomization. Patients will not be allowed to begin a new IP cycle once 2 years after start of IP treatment have elapsed. Therefore, the Treatment Phase is the time period between Day 1 of Cycle 1 and the date of completion of 2 years of therapy, or the trigger date for early end of treatment phase (e.g. occurrence of an iDFS event), including the final assessment 30-42 days thereafter for AE/SAE safety reporting purposes. Study treatment with palbociclib and standard endocrine therapy (if not already started prior to randomization) must begin within 7 days after randomization. This phase is the time period applicable to more “intensive” data collection and required procedures, including physical examination/vital signs, ECOG performance status assessment, adverse events, serious adverse events, IP dispensation, concomitant medications, measurements of treatment adherence(see Section 6.8), laboratory measurements, biospecimens collection (including blood samples as well as samples of local/regional ipsilateral and/or distantmetastatic recurrences and/or contralateral breast cancers, according to the respective guidelines or manuals), recurrence status determination (disease monitoring, see Section 6.2 for details), and PRO assessments (see sections 7 and9).

Patients will continue with the Treatment Phase or begin the subsequent phases under the following conditions:

(1) Begin Follow-Up Phase I upon completion of 2 years of IP treatment in combination with Non-IP therapy (Arm A) or 2 years of Non-IP therapy (Arm B) following randomization.

(2) Continue in Treatment Phase if patient permanently discontinues IP therapy (Arm A) within 2 years of Day 1 of Cycle 1 due to non-iDFS event reasons, but continues Non-IP treatment (see section 10.1). This includes the visits required by the Schedule of Assessments through the completion of this phase. Types of delays or interruptions in IP dosing which will not trigger discontinuation of IP treatment are specified in Section 9.4.2.1.

(3) Begin Follow-Up Phase I if both IP and Non-IP therapy are permanently discontinued within 2 years of Day 1 of Cycle 1 for non-iDFS event related reasons (Arm A). Types of delay in Non-IP therapy that will not trigger permanent discontinuation of Non-IP therapy are described in Section 9.4.1.

(4) Begin Follow-Up Phase I if Non-IP therapy is permanently discontinued within 2 years of randomization for non-iDFS event related reasons (Arm B). Types of delay in Non-IP that will not trigger discontinuation of Non-IP are described in Section 9.4.1.

(5) Discontinue IP therapy, perform an End of Treatment Phase Visit and begin Follow-Up Phase II if patient experiences an iDFS event at any time during Treatment Phase (Arm A).

(6) Patients on Arm B experiencing an iDFS event at any time during Treatment Phase will perform an End of Treatment Phase Visit and begin Follow-Up Phase II.

(7) Randomized patients on either Arm who are deemed ineligible to receive study treatment (IP and/or Non-IP treatment) prior to first dose, or refusing tostart their initial treatment will move to Follow-Up Phase I.

(8) Patients randomized to Arm A, who are deemed ineligible after starting IP therapy may be allowed to continue with IP therapy and remain in the Treatment Phase. However, this is a medical decision that will be made on a case by case basis upon approval after review by regionally assigned medical monitors and using the applicable process described in the Protocol Deviation Management Plan and/or Medical Monitoring Manual for the study. In case the medical monitor decides to stop IP treatment, the patient should begin Follow-Up Phase I.

(9) Patients deemed ineligible after being randomized to Arm B will stop the Treatment Phase and enter into Follow-Up Phase I. However, this is a decision that will be made on a case by case basis upon approval after reviewby regionally assigned medical monitors and using the applicable process described in the Protocol Deviation Management Plan and/or Medical Monitoring Manual for the study.

(10) Patients who are non-compliant or discontinue Study Treatment for non-iDFS event reasons, should be encouraged to complete an End of Treatment Phase Visit and continue participation for long term follow-up and move to Follow-Up Phase I.

(11) Withdrawal of consent for all study participation will end patient activity in the study and clinical follow up.

6.1.3. Follow-Up Phase I

Follow-Up Phase I covers years 3 through 5, after randomization and will begin for both treatment Arms upon completion of the Treatment Phase (e.g. at least 2 years (refer to 6.1.2) after randomization/Cycle 1 Day 1, unless the Treatment Phase ends earlier for non-iDFS event reasons). During Follow-Up Phase I, patient visits should be performed every six months. Half year visits can be performed via phone calls from the site to the patient or provider or as in person visits; yearly visits should be in person. Expected visit dates are calculated based on the randomization date. For patients who terminate the Treatment Phase per protocol, the first Follow-Up visit (Follow-Up Phase I) will be 30 months after randomization (+/- 35 days) and subsequently every six months thereafter until patient completes 5 years after randomization or experiences an iDFS event (→ move to Follow-Up Phase II). For patients who are early end of Treatment Phase for non-iDFS event reasons, Follow-Up Phase I visits may occur at months 6, 12, 18 and 24 after randomization (depending on the actual early end of Treatment Phase date) and until patient completes 5 years following randomization.
Endocrine therapy (Non-IP) is allowed to continue in this phase. Patients will be followed even if endocrine therapy is permanently discontinued. Information collected during this Phase will include: serious adverse events (if related to palbociclib - IP therapy), recurrence status determination (disease monitoring, see Section 6.2 for details), PRO assessments, biospecimens (including samples of local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers, according to the respective guidelines or manuals), and limited information on all breast and/or non-breast anti-cancer related therapies have to be recorded (see section 7).

Patients will continue with Follow-Up Phase I or begin the Follow-Up Phase II under the following conditions:

(1) Once the patient has already entered Follow-Up Phase I, continue with Follow-Up Phase I even if all Non-IP therapies are permanently discontinuedfor non-iDFS event reasons.
(2) Continue with Follow-Up Phase I if patient is deemed ineligible during this phase.
(3) Begin Follow-Up Phase II upon reaching 5 years post randomization without occurrence of an iDFS event.
(4) Begin Follow-Up Phase II if a patient experiences an iDFS event during Follow-Up Phase I.

6.1.4. Follow-Up Phase II

Follow-Up Phase II is the time period where information on extended adjuvant endocrine treatment (more than 5 years) and patient status will be collected annually by in person visits or phone contacts to the patient or provider until a maximum of 10 years after randomization. For patients who terminate the Treatment Phase and Follow-Up Phase I per protocol, the first regular Follow-Up Phase II visit will be 72 months after randomization (+/- 56 days) and subsequent

Follow-Up Phase II visits every 12 months thereafter until a maximum of 10 years after randomization have elapsed.
For patients who are early end of Treatment Phase or early end of Follow Up Phase I for iDFS event reasons, Follow-Up Phase II visits may occur at months 12, 24, 36, 48 and 60 after randomization (depending on the actual early end of Treatment Phase or Follow-Up Phase I date) and annually thereafter until patient completes a maximum of 10 years following randomization. Patients will be followed up even if endocrine (Non-IP) therapy is permanently discontinued. Information collected during this phase includes: serious adverse events (if related to palbociclib – IP treatment), recurrence status determination (disease monitoring, see Section 6.2 for details), biospecimens (including tissue samplesof local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers), and limited information on all breast and/or non-breast anti-cancerrelated therapies have to be recorded (see section 7).

At the visits in year 7 and year 10 collection of additional blood samples is foreseen, to obtain circulating cfDNA as well as plasma samples from all available patients at those time points.

Patients will continue with Follow-Up Phase II if patient experiences an iDFS event during Follow-Up Phase II.

At the conclusion of this phase, or if a patient has withdrawn consent for further participation, patients will be considered to have reached their "End of Study Visit" (section 10) and all new data collection will cease.

6.2. Disease monitoring

All patients, including those who discontinue protocol therapy early, will be followed for oncological events (for details and definitions refer to section 12) and death per ASCO guidelines[63] until the End of Study Visit (a maximum of 10 years after randomization for each single patient).

6.3. Informed Consent

Informed consent form (ICF) may be obtained greater than 30 days before randomization; however, it must be obtained prior to any protocol required assessment (i.e., Screening Phase) which is not performed as part of local routine care.

Signed and dated ICFs for enrolled patients and for patients who are not subsequently screened or randomized will be maintained at the study site. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization.

6.4. Medical History and Demographic Data

Medical history includes clinically significant diseases that are currently active or that

were active, including major surgeries, within the previous 5 years, any cancer history (including prior cancer therapies and procedures) and reproductive status.

Patients may be considered postmenopausal in case that one of the following criteria applies:

- prior bilateral ovariectomy/oophorectomy OR
- Age ≥ 60 years OR
- Age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months* prior to chemotherapy and/or endocrine therapy exposure OR
- Age < 60 years hysterectomized and FSH and plasma oestradiol levels in the post-menopausal range according to local policies prior to chemotherapy and/or endocrine therapy exposure
  *This criterion might not apply to patients younger than 60 years in case they were concurrently using hormone replacement therapy, oral or any other hormonal contraceptives (such as hormonal contraceptive coil etc.).

If none of the above mentioned criteria fully applies, the patient may be judged premenopausal according to local policies. However, in case of any doubts, investigator's judgment on menopausal status is desirable and has to be documented in patient's notes and the eCRF.

Previous type of neoadjuvant and/or adjuvant therapy (i.e. chemotherapy, radiation etc.) including start date and end date must be recorded on the electronic Case Report Form (eCRF) by the investigator or delegate at site.

Demographic data will include age, sex, and self-reported race/ethnicity.

6.5. Reporting of Concomitant Medication

Any concomitant medications and treatments (with the exception of surgery related medication e.g. anesthetics) will be recorded from 30 days prior to randomization and up to the end of the Treatment Phase (refer to 6.1.2 for details).

During the Follow-Up Phases I and II, limited information on all breast and/or non-breast anti-cancer related therapies must be recorded.

6.6. Physical Examination and Vital Signs

At screening, a physical examination including a palpation of breast/chest wall, axillae, supra- and infraclavicular region, height, weight, blood pressure and pulse rate is required.

Symptom-directed physical examinations, blood pressure, weight and pulse rate will be performed at subsequent visits.
All physical examinations and vital signs assessments should be performed by a physician or registered nurse or other qualified health care provider according to local regulations.

6.7. Laboratory Assessments

It is strongly recommended that the following assessments be performed at the research center. If this is not feasible, laboratory tests for individual patients should be performed at the same laboratory. The frequency of assessments is provided in the schedule of assessments (section 7). All initial laboratory assessments during the screening period must be performed within 14 days of randomization.

- Hematology:
  hemoglobin, white blood cell (WBC) count, absolute neutrophils and platelet count.

- Blood chemistry with liver function tests:
  AST, ALT, alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, serum creatinine, total protein and albumin.

- Serum/urine pregnancy test, if required.

Additional hematology/chemistry panels may be performed as clinically indicated. Local laboratory assessments will be performed whenever possible by the same laboratory ("site lab").

HbA_{1C} measurements are mandatory at 5 different time points according to the schedule of assessments. In case of an abnormal value, please refer the patient to a diabetologist, diabetes nurse or locally equivalent medical qualified person for further diagnostic tests and to introduce medication if necessary.

Serum or urine pregnancy test must be negative in women judged premenopausal within 7 days of randomization, or in women with amenorrhea of less than 12 consecutive months at time of randomization. Pregnancy testing does not need to be pursued in patients who are judged as postmenopausal before randomization, as determined by local practice, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation.

6.8. Adherence Measures

Drug Diaries will be maintained for all patients to capture adherence to both oral palbociclib as well as endocrine therapy. Diaries will be completed by the patient and subsequently reviewed for accuracy with the patient at each visit. Pill counts of palbociclib will also be performed and recorded at each study visit by research staff (pill counts for endocrine therapy cannot be performed due to the endocrine therapy being prescribed outside of the study trial). If the patient's pill count of palbociclib is discrepantwith the Drug Diary, the pill count will be used to determine adherence status. Patients found to be non-adherent with their medications may receive additional interventions by the treatment team to improve adherence (i.e. phone calls may be employed as a first-line intervention and extra study visits may be scheduled if non-adherence is still noted at the next three month follow-up timepoint). If a patient demonstrates persistent non-adherence

with endocrine therapy, the provider may stop IP therapy and the patient will be followed per section 6.1.2.

Data from the Drug Diaries will be entered into the eCRF only for those patients who are part of the PRO sample. For each 28 day cycle, data regarding the number of days palbociclib and/or endocrine therapy were taken as well as number of days palbociclib and/or endocrine therapy should have been taken will be entered into the eCRF (adherence to study treatment will ultimately be determined by number of days taken / number of days drug should have been taken over various time points during study).

Patient Self-Reported adherence to oral endocrine therapy and to palbociclib will be assessed separately in a subset of patients.
For that purpose, the 4-item Morisky Medication Adherence scale (MMAS-4) [50,51] has been validated in English, Spanish and German and will be used in a subset of patients from countries with the unique official languages English, Spanish, and German. In addition to the four items of the MMAS-4, an additional question, "All things considered,did you actually take your {Palbociclib/ Anti-hormone pill} exactly as directed by your doctor?" will be asked and translated from English into Spanish and German for the respective Spanish-speaking and German-speaking cohorts. Each item has a Yes/No response format (Yes= zero and No= 1 or one point); scores from the five items will be added to create a composite score ranging from 0 to 5, with a score of 5 considered "mostadherent" (the fifth question added to the MMAS-4 will be reverse-scored).

The 3-item, 6-point Likert McHorney Brief Estimator will also be used to assess patient concerns and importance of adherence[52,53]. The McHorney Brief Estimator will be administered to English-speaking patients in US only.

Both questionnaires (MMAS-4 and McHorney Brief Estimator) will be completed by willing patients within the above defined sub-groups via paper booklet or similar format during planned clinic visits before any procedures/tests are initiated at the site visit and prior to any discussion of their status with healthcare personnel at the site. Questionnaires will be collected at the following time points: on Day 1 of Cycles 2, 3, 6, 12, 18, and 24, as well as at the 36 months (from randomization) visit during Follow-Up Phase I.

6.9. Patient Reported Outcome Measures

In order to evaluate the impact of adjuvant endocrine therapy with or without palbociclib on the QOL of HR+/HER2- breast cancer patients and provide a comprehensive risk benefit assessment that includes the patient perspective in addition to efficacy and safety, below stated questionnaires will be used. These questionnaires were selected to evaluate the impact of treatment and related side effects on symptoms, functioning and global QOL. All questionnaires will be completed by a subgroup of willing patients via paper booklet or similar format during planned clinic visits before any procedures/tests are initiated at the site visit and prior to any discussion of their status with healthcarepersonnel at the site. Questionnaires will be collected at the following time points: on Day 1 of Cycles 1, 2, 3, 6, 12, 18, and 24, as well as at the 36 months (from randomization) visit during Follow-Up Phase I. At each administration time point, it is

anticipated that the questionnaires will take approximately 30-45 minutes for the patients to complete. Questionnaires will be used in a subset of patients from countries with the unique official languages English, Spanish, and German, except for the Breast Cancer Prevention Trial (BCPT) Symptom Scales. Patients may decline to complete a questionnaire at any time. The primary reason for any missed questionnaires will be collected on a case report form.

EORTC QLQ-C30 plus one question from the EORTC QLQ-BR23: The EORTC QLQ-C30 is a well-validated cancer-specific measure[73]. It is comprised of six functional scales (physical, role, emotional, cognitive, social, and global health status/quality of life); three symptom scales (fatigue, pain, and nausea and vomiting); and six single items (appetite loss, constipation, diarrhea, dyspnea, sleep disturbance, and economic consequences of the disease and treatment). Functional and symptom scales/items are combined into a newly developed single health-related QOL (HRQL) summary measure[81,82]. The summary score and all scales and single items range from 0-100. A high score for the summary measure and all functional scales indicates a high/better level of QOL orfunctioning, whereas a high score on a symptom scale/item represents a higher level of symptoms/problems. The questionnaire has been designed for use in international clinical trials and has been developed in multicultural setting which facilitates cross study comparisons. It is available in more than 30 languages. In addition to the EORTC QLQ- C30, a single item measuring alopecia will be used from the EORTC QLQ-BR23. The BR23 is a rigorously developed and tested module commonly administered in patients receiving treatment for breast cancer in addition to the core C30 questionnaire. Like the C30 questionnaire, the BR23 is available in many languages.

Brief Fatigue Inventory (BFI): This questionnaire measures the effect of cancer therapy and the disease itself on fatigue in cancer patients/survivor[74]. It assesses both the severity of fatigue, as well as its impact of daily functioning. It is comprised of 9 questions, and takes 1 minute or less to complete. Both severity and impact of fatigue scores are calculated, with higher scores indicating worse fatigue/impact on daily life. It is available in more than 30 languages.

Brief Pain Inventory (BPI): To quantify arthralgia (joint pain) intensity and pain interference a modified Brief Pain Inventory (BPI) will be used. The BPI is one of the most widely used instruments to measure pain in cancer patients and has been demonstrated to be a reliable, valid, and responsive measure[75]. Since breast cancer patients can have pain other than arthralgia (e.g., post-mastectomy pain, neuropathy), the question will be modified by adding, “pain in and around your joints” to make the items more specific as also done in prior intervention trials[76,77]. To measure patient perceptionof joint pain due to hormonal therapies, a one-item question based on prior work has beendeveloped[78,79]. Participants will be specifically asked to attribute their current joint painto one or more of several listed factors included aging, aromatase inhibitors, other medical conditions, or medications. Patients who reported aromatase inhibitor (AI) as a cause of current arthralgia will be defined as having AI-associated arthralgia. The questionnaire is available in more than 30 languages.

Breast Cancer Prevention Trial (BCPT) Symptom Scales: Three subscales from theBCPT Symptom Scales will be used to assess symptoms related to hormone therapy: hot flashes (2 items), vaginal problems (2 items), and musculoskeletal pain (3 items). Respondents are asked to rate how bothersome these symptoms were in the past 4 weeks on a scale from 0 (not at all), 1 (slightly), 2 (moderately), 3 (quite a bit), 4 (extremely). Single item scores are summed together to create the subscale scores. Higher scores indicate higher levels of bothersome symptoms[80]. The questionnaire will be administered to English-speaking patients in US only.

Additional questions about menstrual function: Three questions are included to assess menstrual function. Specifically, female participants will be asked how often they had their menstrual period on average in the past 6 months (response options: approximately once every month; irregularly but at least once in the past 6 months; or no menstrual periods in the past 6 months). Female participants will also be asked if their menstrual periods have permanently stopped, and if so, the reason. Lastly, female participants will be asked if they have had surgical procedures involving the uterus and/or one or both ovaries. These questions are available in English, German and Spanish and will therefore not be required from any other study participants.

6.10. Study measures implemented during COVID-19 Pandemic

With the outbreak of the COVID-19 pandemic in 2019/2020, which subsequently affected all countries participating in the PALLAS trial, temporary alterations to study measures were implemented to minimize patient risk while safeguarding data documentation related to COVID-19 impact on the PALLAS trial. As communicated in a harmonized "Dear Investigator Letter" and a dedicated, harmonized "Sponsor Memo" thefollowing measures were established during the COVID-19 pandemic:

- Any patient visit described in the PALLAS Protocol, that does not require patients to be in clinic for study assessments, may be carried out remotely.
- For active Arm A patients (receiving IP):
    - Patients should continue to receive routine safety lab and physical exam screenings to establish eligibility for retreatment as described in the PALLAS Protocol, if possible.
    - If hematology cannot be performed, yet the patient is 1) judged to be overall healthy, 2) less than 65 years old and 3) has no history of any Grade 3 neutropenia for (at least) the last 4 Cycles, the onset of the next cycle may be delayed given the unavailability of hematology. Following this a renewed phone interview is to be conducted by investigator (or representative) on the day of delayed cycle start and IP treatment may be continued, if judged to be acceptable by the investigator. To supply patients unable or unwilling to attend visits on site with IP, exceptional site to patient shipments of IP were implemented (see below for details).
    - For any patient who does not fit the above criteria, hematology assessements should be available prior to IP dispensation. Palbociclib intake may be held for a maximum of 8 consecutive weeks considering the exceptional circumstances.
- For Arm B patients and patients in Follow-Up:

  - Visits may be restructured as remote visits as applicable and possible.
- The use of local laboratories and medical centers to perform standard assessments (standard hematology and chemistry tests as well as physical examinations) is exceptionally permitted during the COVID-19 pandemic. Records of these tests must be sent to the treatment site for PI / Co-Investigator review in a timely manner. These assessments should be combined with telephone follow up for data collection and documentation in the eCRF.
- Shipment of Study Drug and Questionnaires:
  - To enable continuous treatment of active Arm A Patients (see above), the controlled shipment of IP from the responsible site directly to the patient is permitted during the COVID-19 pandemic, if patient on site visits are not possible and the patient agrees with this process.
  - Study specific patient paper questionnaires are exceptionally permitted to be sent to patients via e-mail or mail.
- Documentation of COVID-19 related study data:
  - A COVID-19 eForm was generated and implemented to document information on COVID-19 testing, early end of IP/non-IP or early end of study events related to COVID-19. This eForm is to be documented for any patients who are not early end of study by 01 Dec 2019 (time points of assessment are defined in section 7)
  - Any issues or protocol deviations occurring due to the COVID-19 pandemic are to be documented as a COVID-19 related protocol deviation, even if the issue is generally not defined as a protocol deviation.
  - Any remote patient contact or data acquired in such contacts is to be documented in the appropriate sections of the eCRF.
- To maintain sponsor oversight, both sponsors implemented adequate measures and guidance documents on site monitoring processes in line with regulatory requirements.
- All measurements are to be established in line with applicable local laws and regulations in the participating PALLAS countries.

7. Schedule of Assessments

	Screening Phase[a]	Treatment Phase[b]					End of Treatment Phase Visit	Follow-Up Phase I [c, u]	Follow-Up Phase II [c, u]
Patient Visit #	0 (baseline)	1	2[v]	3	4[v]	5-12	13	Q 6 months	Q 12 months
Cycle (C) 1 cycle = 28 Days	0 (baseline)	C1		C2		C3, C6, C9,C12, C15,C18,C21,C24	After C26 or early termination		
Day (D) of Cycle	-30 to 0	D1[d]	D14[v]	D1	D14[v]	D1			
Time Window for Assessments (days) - Arm A		-7	+/-2	-2[n]	+/-2	- 7[n]	30-42	+/- 35	+/-56
Time Window for Assessments (days) - Arm B		+2/ -7	+/-2	+/-2[n]	+/-2	+/- 7[n]	30-42	+/-35	+/-56
Informed Consent[e]	X								
Inclusion/Exclusion Criteria	X								
Medical History & Demographic Data[f]	X								
Concomitant Medications[g]	X	X		X		X	X	X[g]	X[g]
ECOG Performance Status	X	X		X		X	X		
Physical Exam/Vital Signs[h]	X	X		X		X	X		
IP Dispensing; IP and Non-IP Drug Compliance[i]		X		X		X	X[x]		
Adverse Event Reporting[j]	X	X	X[v]	X	X[v]	X	X	X[w]	X[w]
Hematology[k]	X	X	X[v]	X	X[v]	X	X		
Blood Chemistry, with Liver Function Tests[k]	X	X		X		X	X		
Serum/Urine Pregnancy Test[l]	X								
HbA_{1C}[m]	X					X[m] (C6, C12, C18)	X		
Circulating cfDNA[o]		X				X (C6)	X	X (5y)	X (7y, 10y)
Disease Monitoring[p]	X	Patients will be followed per ASCO Guidelines throughout the course of the study.							
Whole Blood (Pharmacogenomic		X		(X)					

	Screening Phase[a]	Treatment Phase[b]					End of Treatment Phase Visit	Follow-Up Phase I [c, u]	Follow-Up Phase II [c, u]
Patient Visit #	0 (baseline)	1	2[v]	3	4[v]	5-12	13	Q 6 months	Q 12 months
Cycle (C) 1 cycle = 28 Days	0 (baseline)	C1		C2		C3, C6, C9,C12, C15,C18,C21,C24	After C26 or early termination		
Day (D) of Cycle	-30 to 0	D1[d]	D14[v]	D1	D14[v]	D1			
Time Window for Assessments (days) - Arm A		-7	+/-2	-2[n]	+/-2	- 7[n]	30-42	+/- 35	+/-56
Time Window for Assessments (days) - Arm B		+2/ -7	+/-2	+/-2[n]	+/-2	+/- 7[n]	30-42	+/-35	+/-56
Sample)[q]									
Serum		X							
Plasma[o]		X				X (C6)	X	X (5y)	X (7y, 10y)
Tumor Tissue[r]	X	In case of local/regional ipsilateral and/or distant disease recurrences and/or contralateral breast cancers, biopsies of these lesions are strongly encouraged.							
PRO Questionnaires[s]		X		X		X (C3, C6, C12, C18, C24)		X[s]	
Adherence Questionnaires[t]				X		X (C3, C6, C12, C18, C24)		X[t]	
COVID-19 related assessment							X[y]	X[y]	X[y]

Table 2: *Schedule of Assessments*

a) Screening Phase: All screening evaluations must be completed and reviewed to confirm that patients meet all inclusion criteria and do not meet any of the exclusion criteria before randomization.

b) Treatment Phase: Non-IP (if not already started) and IP therapy must start within 7 days after randomization. All assessments should be performed prior to dosing with IP (palbociclib) or Non-IP (endocrine therapy) on the visit day, unless otherwise indicated. The Schedule of Assessments during this planned 2 year period (including a visit at 30-42 days after completion of 2 years of therapy or after trigger date for early end of treatment phase for a final safety assessment) applies to both arms. IP treatment is to be given for 2 years, which is a total of twenty-six 28-days cycles (for patients without interruptions or delays). The goal is not to administer a specific number of cycles, but to allow for completion of a cycle if it started prior two years from randomization. Patients will not be allowed to begin a new IP cycle once 2 years after start of IP treatment have elapsed.

c) Follow-Up Phases I & II: Half year visits can be performed via phone calls from the site to the patient or the provider, or as in person visits; yearly visits should be in person during Follow-Up Phase I. During Follow-Up Phase II, annual patient contacts shall be performed by in person visits, or phone contacts to the patient or the provider (except FU II Visit year 7 and 10 where blood samples should be collected). See section 6.1 to make determinations how the patient will move through the Follow-Up I and Follow-Up II phases of the study for assessments, data collection, and follow-up for the study. Appendix B further describes these phases.

d) If screening assessments occur within 7 days before Cycle 1 Day 1, then they may serve as the Cycle 1 Day 1 assessments also and do not need to be repeated.

e) Informed consent form may be obtained greater than 30 days before randomization; it must, however, be obtained prior to any protocol required assessment (i.e., Screening Phase) which is not performed as part of local routine care.

f) Medical history includes clinically significant diseases that are currently active or that were active, including major surgeries, within the previous 5 years, any cancer history (including prior cancer therapies and procedures) and reproductive status. Demographic data includes age, sex and self-reported race/ethnicity. In addition, stratification factors will be assessed.

g) Any concomitant medications and treatments will be recorded from 30 days prior to randomization and up the end of the Treatment Phase (refer to section 6.1). During the Follow-Up Phase I and II, only limited information on breast and/or non-breast anti-cancer related therapies have to be recorded. Endocrine therapy is not considered concomitant medication and has to be recorded separately with detailed data capture during the Treatment Phase.

h) At screening, a physical examination including a palpation of breast/chest wall, axillae, supra- and infraclavicular region, height, weight, blood pressure and pulse rate is required. Symptom-directed physical examinations, blood pressure, weight and pulse rate will be performed at subsequent visits.

i) IP dispensation (palbociclib) will take place at each Cycle Day 1 onsite visit. Patients will receive amount of IP in order to ensure sufficient supply until the next scheduled Cycle Day 1 onsite visit. Drug Compliance for IP will be assessed by drug accountability (patients are requested to return any used and unused bottles of IP at their next scheduled onsite visit). Furthermore, patients are requested to complete IP Drug Diaries, which also have to be returned at each onsite visit. At each visit, prior to IP dispensation, an AE and laboratory based assessment has to be performed by the investigator for evaluation of potential dose reduction obligations according to the protocol. There will be no drug accountability for Non-IP. However, compliance will be assessed at each patient onsite visit via Non-IP Drug Diaries completed by the patients. Patients are requested to bring Drug Diaries back to the site at each visit. IP Drug Diaries and/or Non-IP Drug Diaries should be collected during the treatment phase of the study.

j) AEs/SAEs must be reported from the date of signature of informed consent form for all enrolled patients, until the last visit of the Treatment Phase (see section 6.1.1 and section 10.1). During the Screening Phase, only Adverse Events deemed to be serious (SAEs) and related to any study mandated and not routinely performed procedures must be reported to the appropriate study Sponsor. SAEs must be reported within 24 hours of site awareness (see section 11.6. for further instructions). AEs fulfilling the criteria for expedited reporting have to be treated according to the reporting procedures described in section 11 including a submission to the respective Sponsor within 24 hours of awareness.

k) Hematology includes hemoglobin, white blood cell count (WBC), absolute neutrophils, platelet count. Blood chemistry includes AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, total calcium, total bilirubin, serum creatinine, total protein and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. It is strongly recommended that all assessments will be performed at the research center. If this is not feasible, laboratory tests for individual patients should be performed at the same laboratory. During the Screening Phase, all laboratory assessments must be performed within 14 days of randomization.

l) Serum or urine pregnancy test must be performed and negative for women of childbearing potential (≤ 7 days prior randomization). Testing may be repeated on a regular schedule as per request of IRB/IECs or if required by local regulations.

m) HbA_{1c} will be measured at Screening, Day 1 of Cycles 6, 12, and 18 and at the End of Treatment Phase Visit. In case of an abnormal value, please refer the patient to a diabetologist or a diabetes nurse for further diagnostic tests and to introduce medication if necessary.

n) Time window does not apply to patients experiencing AE induced dose delays at the start of a cycle.

o) Blood samples for the assessment of circulating Cell-Free DNA and Plasma samples will be collected from all patients, at Cycle 1 Day 1, Cycle 6 Day 1, at the end of Treatment Phase Visit, at 5 years after randomization and at the time of ipsilateral local/regional and/or distant recurrence and/or contralateral breast cancer, unless prohibited by local regulations. For details refer to table 3.

p) Information will be collected on date and site of all recurrences, all endocrine, all cytotoxic (+/- targeted) treatment, date and cause of deaths as well as date and diagnosis of secondary malignancies.

q) Whole blood sample for pharmacogenomic research should be either collected at C1D1 or C2D1. Only applicable for patients who agreed (prior to sample collection) to donate blood samples for the purpose of pharmacogenomic analyses, if required according to local regulations.

r) Representative tumor tissue FFPE block from surgery or from diagnostic core biopsy is to be collected. Receipt of FFPE tumor tissue block at the central sample repository is required for patient randomization (see section 8.2.1). Tissue banking will be required for translational endpoint analyses. Local ER+ and/or PR+ as well as HER2- results will be used for the purpose of eligibility (according to local standards; Cut-off values for positive/negative staining should be in accordance with current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines). Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment. If a patient develops local/regional ipsilateral recurrences and/or distant recurrences and/or contralateral breast cancer,every effort should be made to collect a tumor sample from the sites of these oncological events. Details on preparation of these samples including processing, storage, and shipment will be provided in separate guidance documents.

s) Following PRO measures will be used: EORTC QLQ–C30 plus one question from the EORTC QLQ-BR23, Brief Fatigue Inventory (BFI), Brief Pain Inventory (BPI), Breast Cancer Prevention Trial (BCPT) symptom scale, and additional questions about menstrual status; these will be collected on Day 1 of Cycles 1, 2, 3, 6, 12, 18, and 24, as well as at the 36 month visit (i.e., visit that is approximately 36 months after randomization) during Follow-Up Phase I. Questionnaires will be used in a subset of patients from countries with the unique official languages English, Spanish, and German except for the BCPT symptom scale which will be administered to English-speaking patients in US only.

t) Two questionnaires for Adherence will be collected on day one of cycles 2, 3, 6, 12, 18 and 24, as well as at the 36 month visit (i.e., visit that is approximately 36 months after randomization) during follow up phase I. The McHorney Brief Estimator will be administered to English-speaking patients in US only. The Morisky Scale will be used in a subset of patients from countries with the unique official languages English, Spanish, and German.

u) In Follow-Up I and II, extended adjuvant endocrine treatment (more than 5 years) is allowed and limited information should be documented within the medical records for subsequent data submission via Case Report Forms.

v) Visits 2 and 4 (C1D14 and C2D14) can be telephone contacts for all patients, and can occur +/- 2 days around Day 14. All patients in both arms should have AEs collected on the calls. Patients in Arm A only will have safety laboratory testing performed for these Visits; laboratory testing must be performed at the research center, and the Visit 2 and 4 telephone calls should occur after the laboratory testing is resulted. Laboratory testing for Arm B is at the discretion of the provider.

w) During Follow-Up Phases I and II only newly occurred serious adverse reactions (SARs) related to palbociclib have to be documented on the SAE form and have to be submitted to the respective Sponsor within 24 hours of site awareness. Serious adverse events occurring to a patient after the Treatment Phase has ended (i.e., during the Follow-Up Phases I & II) should be reported to the

respective Sponsors if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes to have at least a reasonable possibility of being related to palbociclib are to be reported to the respective Sponsor.

x) No IP will be dispensed at this visit but only drug diaries collected.

y) A COVID-19 related assessement (including data on COVID-19 testing, early end of IP/non-IP and early end of study) is to be perfomed and documented in the appropriate eForm for any patient who was not early end of study by 01 Dec 2019.

8. Data and Specimen Submission

For COVID-19 related measures implemented regarding data collection, please refer to section 6.10.

8.1. Data Collection and Submission

The site will be supplied with the following data collection tool: a web browser address for an Electronic Data Capture (EDC) system database that has been fully validated and conforms to 21 CFR Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. The EDC system databases will be maintained by Alliance Foundation Trials (AFT) for the US and by ABCSG for the Non-US sites. Periodically throughout the duration of the trial and at the completion of the trial, the US and Non-US sites databases will be merged to facilitate analysis of the complete trial dataset.

The trained Investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture forms as needed) into the EDC system. All information on the eCRFs must be traceableto these source documents. Data recorded directly on the eCRFs will be defined before study start. eCRFs will be completed for all subjects randomized to study treatment. eCRFs for subjects who are randomized but not treated will be completed with all data collected at the time of subject study discontinuation. A Clinical Monitor will review the eCRFs entered by investigational staff for completeness and accuracy according to respective trial monitoring plan.

Automatic validation programs or manual checks for data discrepancies in the eCRFs may result in electronic queries generated for resolution by the investigational site. Designated investigator site staff is required to respond to these queries and make any necessary changes to the data.

During the Screening Phase, only AEs deemed to be serious (SAEs) **and** related to protocol mandated and not routinely performed procedures have to be reported.
All treatment-emergent AEs (events occurring from the first dose of study medication during the Treatment Phase until the end of safety reporting period (30 to 42 days after completion of 2 years of therapy or after trigger date for early end of treatment phase)) will be recorded. AEs will be coded using the *MedDRA* dictionary. Concomitant medications will be coded using a standard dictionary (e.g. WHODrug).

Audits for quality assurance of the database may be performed according to relevant Standard Operating Procedures within the respective Sponsor.

8.2. Specimen Collection and Submission

Table 3 summarizes the biospecimens that are to be collected from participants, with reference to specific study time points. All biospecimen collections are mandatory, unless otherwise specified and/or specifically prohibited by local regulations or patient refusal. Specific instructions for the collection, on-site processing, and shipment of biospecimens is provided in the TRANS-PALLAS Investigator Manual of Procedures and the sample management guidelines and/or manuals.

Location of central tissue and blood specimen repositories, as well as logistical pathways for on-site processing and shipping of biospecimens will be different for US and Non-US sites. Details and instructions will be provided to the sites by the respective study Sponsor via separate sample management guidelines and/or manuals, including the TRANS-PALLAS Investigator Manual of Procedures. Following site request, the submitted FFPE tumor tissue block will be returned to the site.

8.2.1. Tumor and Blood Specimen

An archival, formalin-fixed paraffin-embedded (FFPE) tumor tissue BLOCKmust be available and received at the central sample repository for EACH patient PRIOR TO RANDOMIZATION. Sample shipment to the respective central sample repository may only be performed following patient consent and allocation of the study specific patient identification number via IxRS.

An FFPE block containing representative tumor tissue from a surgical specimen is requested from patients who have completed surgery prior to adjuvant systemic therapy. For patients who received preoperative/neoadjuvant systemic therapy, both pre-treatment diagnostic core biopsy samples and post-treatment surgical specimen are requested. If only one sample can be sent, then the pre- treatment tissue remains the first priority – to be consistent with the samples from the adjuvant setting – but post-treatment tumor tissue is acceptable as a second priority.

Details on block selection, preparation, and shipment are found in the TRANS-PALLAS Investigator Manual of Procedures and the sample management guidelines and/or manuals.

Once patient eligibility has been established and after receipt of adequate tissue at the central sample repository, the site will be authorized to randomize the respective patient into the study. Patients who have passed eligibility screening, but for whom no adequate FFPE tissue block has been received by the central sample repository, may not be randomized into the study. Sites will have the possibility to re-send a replacement specimen, in order to randomize the patient to the study.

Although confirmed receipt of tumor tissue (without any quality check prior to randomization) at the central sample biorepository is sufficient to enable patient

randomization, site will be requested to re-send a further sample if the initial sample is inadequate. Patients who have passed eligibility screening and submitted an FFPE block to the central sample repository, but for whom the FFPE tissue block was found to be not adequate prior to randomization, may be randomized into the study. However, in this situation, sites are requested to senda replacement specimen to ensure that adequate tissue is available. The randomization will not be delayed by the shipment of this additional sample.

Central confirmatory immunohistochemical review (e.g. ER, PR or HER2 testing) of the tumor block will not be performed.
If available, a baseline sample of fresh or frozen tumor tissue may be provided as well. This sample is optional, and does not replace or substitute for the required FFPE tissue sample. Details on sample selection, preparation, and shipment are found in the TRANS-PALLAS Investigator Manual of Procedures and the sample management guidelines and/or manuals.

Sample Type*	Screen-ing	Cycle 1, Day 1	Cycle 6, Day 1	End of Treat-ment Phase Visit**	5 years**	7 years**	10 years**	At the time of local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers
FFPE tumor tissue	X							X***
Serum		X						
Plasma		X	X	X	X	X	X	X
Whole Blood (Pharmacogenomic Sample)		X****						
Circulating cfDNA		X	X	X	X	X	X	X
Frozen/fresh tumor tissue or nucleic acids		X*****						X*****

Table 3: *Tissue/Samples for TRANS-PALLAS translational research*

* See TRANS-PALLAS Investigator Manual of Procedures for further details on tube selection and specimen shipping.

** Not required if patient experienced prior local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers and related blood draws have occurred (at the earliest possible occasion).

*** Tissue sampling at the time of local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers is strongly encouraged not only to confirm disease, but also to provide a sample for the biorepository. It does not necessarily need to be a FFPE sample but can be other sample type as described in the TRANS-PALLAS Investigator Manual of Procedures.

**** Whole blood sample for pharmacogenomic research should be either collected at C1D1 or C2D1.

***** Optional samples, to be sent only if available.

9. Study Treatment

9.1. Study Treatment Overview/Terms and Descriptions

IP Treatment is comprised of palbociclib treatment for 2 years (refer to 6.1.2) for patients randomized into Arm A.

Non-IP Treatment is comprised of standard endocrine therapy for at least 5 years for patients randomized into Arm A and B.

Palbociclib is the only *investigational product (IP)* of this trial and will be provided free of charge by the Sponsors.

Protocol approved adjuvant endocrine therapy regimens (also referred to as background treatment) are considered *Non-IP* as they represent routine or standard of care treatment for the respective patient population. Endocrine therapy will not be provided by the Sponsors and must be selected by the Investigator as part of a standard of care therapy.

9.2. Palbociclib - Investigational Product (IP)

9.2.1. Palbociclib – Formulation, Packaging and Labeling

Palbociclib Drug Substance and Drug Product are manufactured, labelled and packed according to current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines for use in the clinical studies. Each lot of palbociclib for clinical studies is subjected to a series of quality control tests to confirm its identity, purity, potency, and quality.

Palbociclib will be manufactured by Pfizer and provided by the study Sponsors as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. Palbociclib will be supplied to sites in High Density Polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules and are labelled for clinical use. The capsules can be differentiated by their size and color (seebelow).

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel	0

Table 4: *Palbociclib capsule characteristics*

9.2.2. Palbociclib – Storage, Handling and Processing

Palbociclib capsules should be stored at controlled and monitored room temperature (15-30°C, 59-86°F) in their original container. Further storage and stability conditions are stated in the palbociclib IB. Investigators and site staff are requested to check storage temperatures on working days (i.e. manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products.

Deviations from the storage requirements, including any actions taken, must be documented and reported to the respective study Sponsor – to AFT for US sites and to ABCSG for Non-US Sites. Once a deviation is identified, palbociclib must be quarantined and not used until receipt of documentation of permission to use the investigational product.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Medication which has been returned by the patients should be stored separately from medication that needs tobe dispensed.

9.2.3. Palbociclib – Dosing and Administration

Palbociclib should be taken orally, once per day with food. Treatment is continuous daily for 21 days, followed by 7 days off, to complete a 28 day cycle. Details can be found in table 5.

Expected toxicities and potential risks as well as allowable dose modifications are described in section 9.4. No investigational or commercial agents or therapiesother than those described below may be administered with the intent to treat the participant's malignancy within the treatment phase.

Administration is performed on an outpatient, self-administration basis. At the beginning of the new cycle, the patient should not take scheduled palbociclibdose before all visit assessments have been performed (and are within acceptable range) unless otherwise indicated.

Missed doses of palbociclib should not be made up. For example, if a dose is vomited any time after taking palbociclib, a replacement dose should NOT be taken. If a dose is entirely missed for one day, dose should be skipped and NOT retaken the next day; patients should resume regular dosing as prescribed the following day. Patients who inadvertently take 1 extra dose during a day must skip the next day's dose. If patient takes more than two doses of palbociclib in a day, the patient should bring this to the attention of his or her treating physician.

Patients should be instructed to record daily administration of the study drugs in a drug or medication diary.

9.2.4. Palbociclib – Dispensation and Accountability

The study IxRS system will be used by clinical sites to acknowledge receipt of study drug. Damaged shipments will be replaced.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit and should further be instructed to keep their medication in the bottles provided and not transfer it toany other container. Due to possible unknown hazards associated with topicaland environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only a single capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously received and unused medication to the site and new capsules will be dispensed.

For COVID-19 related measures implemented regarding IP dispensation, please refer to 6.10.

To ensure adequate records and patient compliance monitoring, palbociclib capsules will be accounted for by the site as instructed by the respective study Sponsor. Hence, the site must maintain a careful record of the inventory and disposition of the agent. Accurate records of all IPs received at, dispensed to, returned from, returned to, and disposed of by the study site should be recorded as instructed by the respective study Sponsor.

Patients will be instructed to return previously dispensed bottles (including unused drug and/or empty bottles) as well as their completed palbociclib Drug Diary to the clinic at each visit for accountability purposes even if they will notbe issued with new medication at that visit. Unused returned medication MUST NOT be re-dispensed to patients. The number of remaining capsules/tablets will be documented and recorded within the eCRF. Drug accountability for palbociclib will be performed at each study visit prior to dispensing drug supply for the next cycle(s).

9.2.5. Palbociclib – Destruction and Return

Sites will have to destroy or return unused investigational product(s). The site's principal investigator must ensure that any materials are destroyed or returned in compliance with applicable environmental local regulations, institutional policy, and any special instructions provided by the respective study Sponsor. The site's method of IP destruction must be agreed to by the Sponsor in writing. Verification of drug accountability by the monitor has to be completed before

any IP is destroyed at site. Destruction or return of investigational product must be adequately documented.

9.3. Endocrine Therapy - Non-Investigational Product (Non-IP)

Current treatment guidelines recommend adjuvant standard endocrine treatment for 5 to 10 years for patients with HR+ breast cancer. Adjuvant endocrine treatment might have already started before the patient enters the study. However, initiation of standard adjuvant endocrine therapy must not be more than 6 months before randomization (for details please refer to the inclusion / exclusion section 4).

The following Standard Endocrine Treatment agents (also referred to as background treatment) are allowed for Arm A and Arm B:

- Tamoxifen for pre- and postmenopausal women, as well as men.
- Non-steroidal aromatase-inhibitors (anastrozole, letrozole) for postmenopausal women.
- Steroidal aromatase inhibitor (exemestane) for postmenopausal women.
- LHRH agonists in combination with tamoxifen or AI for premenopausal women and men.
- Surgical or radiologic ablation of the ovaries is also allowed, but additional endocrine treatment has to be given to these patients. Radiologic ablation of the ovaries cannot substitute for LHRH agonist if AI is being used in a premenopausal patient.

Locally obtained commercial supply of tamoxifen, anastrozole, letrozole, exemestane or LHRH agonists will be administered to the patients at the discretion of the principal investigator (or his/her designee) as well as according to standard institutional or regional practice. Generics are allowed, if locally available.

Administration is performed on an outpatient, self-administration basis according to local requirements and local standard practice.

Recommended dosing regimes of oral endocrine therapy are:

- Letrozole: 2.5 mg orally, once a day
- Anastrozole: 1 mg orally, once a day
- Exemestane: 25 mg orally, once a day
- Tamoxifen: 20 mg orally, once a day

Injection of LHRH agonist is allowable on study. If a premenopausal woman or a male patient is receiving LHRH agonist and AI, it is recommended that she/he receives monthly injections rather than every-3-month depot injections. Details for dosing regimes for Arm A and B can be found in table 5 below.

Specific storage conditions, handling dispensation and administration instructions have to be locally followed according to local regulations and in accordance with respective local package inserts and/or local SmPCs.

Expected toxicities and potential risks can be obtained from respective local pack inserts and/or local SmPCs. Allowable dose modifications are described in section 9.4.1.

Missed doses of endocrine therapy should not be made up.

If a patient encounters difficulty tolerating endocrine therapy, the treating provider should make all possible efforts to continue the patient on adjuvant endocrine therapy, including the use of short drug holidays and rotation among endocrine agents, while continuing treatment with palbociclib. If the patient is on Arm A and despite best efforts is unable to tolerate endocrine medication altogether, the patient must then stop palbociclib treatment. If palbociclib is stopped for a patient on Arm A due to reasons other than iDFS events, it is strongly recommended that the patient resumes endocrine therapy once symptoms resolve, or changes to alternative endocrine therapy. See section 6.1 and 7.0 for the schedule of assessments and follow-up. Rotation of AItherapy among the three approved agents is also allowed, as is change to AI from tamoxifen or change to tamoxifen from AI.

Patient adherence to protocol therapy is described in section 6.8.

One treatment cycle = 28 days for data collection purposes. If the patient does not discontinue the Treatment Phase early, a total of 26 cycles of IP and/or Non-IP treatment should be given in the first 2 years (refer to 6.1.2) of study participation. However, missed cycles will not be made up and all palbociclib intake will cease at approximately 2 years. Endocrine therapy should continue per standard of care.

Treatment Description Arm A						
Agent	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**	**Duration**
Palbociclib	Given with food	125 mg	PO	Once Daily on days 1-21, followed by 7 days off	28 days (4 weeks)	~ 2 years
One of the following agents for **postmenopausal women:** (1) Letrozole (2) Anastrozole (3) Exemestane **Pre- and postmenopausal women and men** (4) Tamoxifen	(1) None for letrozole (2) None for anastrozole (3) suggested to take after a meal for exemestane (4) None for tamoxifen	(1) Letrozole 2.5 mg, or (2) Anastrozole 1 mg, or (3) Exemestane 25 mg, or (4) Tamoxifen 20 mg	(1) PO (2) PO (3) PO (4) PO	Once Daily on days 1-28 (continuous)		At least 5 years
Additionally allowed for **premenopausal women and for men:** LHRH Agonist in combination with tamoxifen or AI			SC IM	Recommended once monthly injection in combination with tamoxifen or AI		At least 5 years

Treatment Description Arm B						
Agent	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**	**Duration**
One of the following agents for **postmenopausal women:** (1) Letrozole (2) Anastrozole (3) Exemestane **Pre- and postmenopausal women and men** (4) Tamoxifen	(1) None for letrozole (2) None for anastrozole (3) suggested to take after a meal for exemestane (4) None for tamoxifen	(1) Letrozole 2.5 mg, or (2) Anastrozole 1 mg, or (3) Exemestane 25 mg, or (4) Tamoxifen 20 mg	(1) PO (2) PO (3) PO (4) PO	Once Daily on days 1-28 (continuous)	28 days (4 weeks)	At least 5 years
Additionally allowed for **premenopausal women and for men:** LHRH Agonist in combination with tamoxifen or AI			SC IM	Recommended once monthly injection in combination with tamoxifen or AI		At least 5 years

Table 5: *Study treatment administration and dosing schedule for Arm A and Arm B*

9.4. Dose and Treatment Modifications

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of palbociclib and/or endocrine therapy may need to be adjusted as described below.

Incidence, nature, and severity of adverse events triggering dose or study treatment modifications are to be assessed by the investigator and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v4.0) as AE related dose and treatment modification recommendations arebased on this grading scale.

9.4.1. Dose Modifications / Toxicity Management – Endocrine Therapy

No dose reduction for endocrine therapy is permitted, but dosing interruptions are allowed. Endocrine treatment interruptions for up to 4 consecutive weeks (per

treatment year) for endocrine therapy-related toxicities or personal reasons are allowed as per the investigator's best medical judgment.

However, no more than 6 cumulative weeks off endocrine therapy is recommended per treatment year on study. Subjects missing more than 6 cumulative weeks of endocrine therapy (per treatment year) during the treatment phase of the study will be removed from active treatment phase of the study and will stop IP treatment. Patients who discontinue study treatment (i.e. palbociclib and endocrine therapy for Arm A or endocrine therapy for Arm B) will continue to be followed according to post treatment follow up as defined in Schedule of Assessments (section 7), section 6.1 and Appendix B.

Rotation of AI therapy among the three approved agents is also allowed, as is change to AI from tamoxifen or change to tamoxifen from AI.

If a patient encounters difficulty tolerating endocrine therapy, the treating provider should make all possible efforts to continue the patient on adjuvant endocrine therapy, including the use of short drug holidays (as described above) and rotation among endocrine agents, while continuing treatment with palbociclib. If the patient is on Arm A and despite best efforts is unable totolerate endocrine medication altogether (meaning permanent discontinuation of endocrine treatment), the patient must then stop palbociclib treatment. If palbociclib is stopped for a patient on Arm A, it is strongly recommended thatthe patient resumes endocrine therapy once symptoms resolve, or change to alternative endocrine therapy.

Patients who discontinue study treatment (i.e. palbociclib and endocrine therapy for Arm A or endocrine therapy for Arm B) will continue to be followed according to post treatment follow up as defined in Schedule of Assessments (i.e., also see Follow-Up Phases in section 6.1).

9.4.2. Dose Modifications / Toxicity management – Palbociclib

Dose or treatment modifications for palbociclib are allowable and may occur as *dose interruptions* (within a cycle), *dose delays* (between cycles) or *dose reductions*.

In the event of significant palbociclib treatment-related toxicity, palbociclib dosing may be interrupted or delayed or reduced as described within this section and according to table 7.

In the event of multiple toxicities, dose modification should be based on theworst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Dose Reductions Section (see section 9.4.2.3)

unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied, the patient may need to return to the clinic to receive new drug supply.

9.4.2.1. Palbociclib Dosing Interruptions/Delays

In general, cycles should be 28 days long unless the start of a new cycle is delayed and palbociclib intake may not be interrupted/delayed formore than 4 consecutive weeks due to reasons other than surgery (referto section 9.5.1) or IP-related adverse event (refer to section 9.4.2.2).

Doses missed within a cycle (meaning dose interruptions) are not made up. If, e.g. the AE resolves before the end of the cycle, then the patient can resume taking the palbociclib for the remainder of the cycle but should still stop on Day 21 to maintain the 7- day break.

The start of a new cycle should be delayed according to guidelines within this section, if an adverse event requiring a dose hold has not resolved by Day 1 of the next planned cycle.

Patients on Arm A, experiencing one or more of the following adverse events should have their palbociclib treatment interrupted/delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia (ANC < 1000/mm^3).
- Grade 3 or 4 neutropenia (ANC < 1000/mm^3) associated with a documented infection or fever >38.3 C (101 F) or a sustained temperature of ≥ 38 C (100.4 F) for more than one hour.
- Grade 3 or 4 thrombocytopenia (Platelet count < 50,000/mm^3)
- Grade ≥ 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment).
- Grade 2 non-hematologic toxicity persisting despite optimal medical treatment, lasting more than 3 weeks, and unacceptable to patient and/or provider.
- In case of concurrent occurrence of > 3x ULN ALT and 2x ULN Total Bilirubin, at any time during the trial, palbociclib will be permanently discontinued.

Patients should not hold or discontinue palbociclib for side effects potentially or likely related to concomitant standard endocrine therapy (e.g., grade 3 or long lasting grade 2 joint pain) as per the investigator's judgment.
Follow up assessments according to investigator's decision should be performed until adequate recovery occurs as assessed by the Investigator.
If a patient finds oneself not able to tolerate endocrine therapy, an attempt to change to an alternative endocrine therapy is a priority, while

continuing treatment with Palbociclib, if on Arm A with the alternative endocrine therapy. If patient is considering stopping endocrine medication altogether, if on Arm A the patient must stop palbociclib treatment. For a patient who chooses to stop palbociclib, it is strongly recommended to encourage the patient to resume endocrine therapy oncesymptoms resolve, or change to alternative endocrine therapy. Patients who discontinue study treatment (i.e. palbociclib and endocrine therapy for Arm A or endocrine therapy for Arm B) will continue to be followed according to post treatment follow up as defined in Schedule of Assessments (section 7), section 6.1 and in the Appendix B.

9.4.2.2. Palbociclib Retreatment Criteria

Retreatment with palbociclib following treatment interruption or delay for treatment related toxicity at the start of a new cycle that requires a clinic visit (day 1 of cycles 2, 3, 6, 9, 12, 15, 18, 21, 24) may not occur until all of the following parameters have been met:

- Platelet count ≥ 75,000/mm^3;
- ANC ≥ 1000/mm^3 and no fever;
- Any persistent grade 2, grade 3 or higher treatment-related non-hematologic AEs considered related to palbociclib have recovered to Grade ≤ 1 or baseline, or Grade ≤ 2 (if not considered a safety risk for the patient)

The start of new cycles that do not require a clinic visit may begin without receiving laboratory results for additional laboratory tests. Study site should contact the patient when the laboratory results are available to instruct the patient to modify treatment if abnormal laboratory results requiring treatment hold are noted. Laboratory results must be available by Day 3 of each cycle where required. Whenever retreatment after dose delay occurs, the first palbociclib dosing day would count as Day 1 of the cycle.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be adjusted as clinically indicated.

If the retreatment parameters are met within 4 weeks of treatment interruption or cycle delay, palbociclib may be resumed. Please refer to Dose Reductions Section 9.4.2.3 for adverse events requiring dose reduction at the time of treatment resumption. Please note that if a cycle is delayed for more than 27 days, it is seen as a missed cycle and must be documented as not started.

If these parameters have not been met after 4 weeks of dose interruption (including the scheduled 1 week off treatment) or cycle delay, the patient should permanently discontinue palbociclib treatment.

9.4.2.3. Palbociclib Dose Reductions

- The palbociclib dose may need to be reduced, following a dose interruption or cycle delay when treatment is resumed.
- No specific dose adjustments are recommended for Grade 1 or short lasting Grade 2 (< 4 weeks) treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances and document the changes in the CRF.
- For palbociclib related, Grade 2 toxicity lasting for ≥ 4 weeks (excluding alopecia) or for palbociclib related Grade 3 toxicities (despite maximum supportive care as judged by the investigator), palbociclib dose reduction is recommended for all subsequent cycles. Taking palbociclib according to recommendation (i.e., with food) should be reinforced and confirmed. Dose reduction of palbociclib by one dose level, and, if needed, by two dose levels (Table 6) may be required depending on type and severity of the toxicity encountered. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalations are not allowed. Patientsrequiring more than 2 dose reductions will discontinue palbociclib treatment and should stay in treatment phase as long as endocrine treatment is not discontinued (per section 6.1.2).

Dose Level	**Palbociclib once daily on days 1-21, followed by 7 days off**
Starting dose	125 mg/d
Level -1 (first dose reduction)	100 mg/d
Level -2 (second dose reduction)	75 mg/d
Discontinue palbociclib treatment	

Table 6: *Palbociclib Dose Levels and Dose Reduction Schedule*

CTCAE v.4.0 Adverse Event	CTCAE v.4.0 Grade	Intervention with Palbociclib
Febrile neutropenia (Neutropenic fever)	3, 4	*Hold until clinically stable, if ANC recovers (ANC ≥ 1000/mm^3) and absence of fever,* then *1st appearance:* resume at next lower dose *2nd appearance:* resume at next lower dose *3rd appearance:* Discontinue
Neutrophil count decreased *(Note: The use of growth factors is not recommended)*	3	*Hold until ≥ 1000/mm3,* then *1st appearance*: resume at same dose level *2nd appearance:* resume at next lower dose *3rd appearance:* resume at next lower dose *4th appearance:* Discontinue
	4	*Hold until ≥ 1000/mm3*, then *1st appearance*: resume at next lower dose *2nd appearance:* resume at next lower dose *3rd appearance:* Discontinue
Platelet count decreased	3	*Hold until ≥ 75000/mm3*, then *1st appearance:* Maintain dose *2nd appearance:* resume at next lower dose *3rd appearance:* resume at next lower dose *4th appearance:* Discontinue
	4	*Hold until ≥ 75000/mm3*, then *1st appearance:* resume at next lower dose *2nd appearance:* resume at next lower dose *3rd appearance:* Discontinue
Anemia	3, 4	*Reduce to next lower dose only in cases of protracted symptomatic anemia considered to be related to palbociclib*
Alanine aminotransferase (ALT) increased with total bilirubin < 2X ULN (in the absence of cholestasis or hemolysis)	3	*Hold until clinically stable and recovered to ≤ Grade 1 or to baseline,* then *1st appearance:* resume at same dose *2nd appearance:* resume at next lower dose *3rd appearance:* Discontinue

CTCAE v.4.0 Adverse Event	CTCAE v.4.0 Grade	Intervention with Palbociclib
Alanine aminotransferase (ALT) increased with total bilirubin < 2X ULN (in the absence of cholestasis or hemolysis)	4	*Hold until clinically stable and recover to ≤ Grade 1 or has returned to baseline,* then *1st appearance:* resume at next lower dose *2nd appearance:* discontinue
Concurrent > 3 X ULN ALT (SGPT) and 2 X ULN total bilirubin		Discontinue immediately
Other AEs requiring dose modification per investigator *(Note: Investigator must determine attribution of AE and only follow dose modifications for the causal agent.)*	2	*Lasting Less than 4 weeks*: Maintain Dose *Lasting 4 weeks (excluding alopecia) or more despite maximal supporting care unacceptable to patient and/or investigator, and thought to be related to palbociclib*: resume at next lower dose
	3, 4	If the AE is related to palbociclib, withhold until symptoms resolve to: • ≤ Grade 1 or to baseline • ≤ Grade 2 (if not considered a safety risk for the patient) Resume at the next lower dose level.
Hepatic impairment	Please refer to the Child-Pugh classification described in the right column	No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of palbociclib is 75 mg once daily.
Interstitial Lung Disease (ILD) or pneumonitis *(Note: Please monitor patients regularly for pulmonary symptoms indicative of ILD/pneumonitis. Signs and symptoms may*	2	Interrupt palbociclib immediately in patients who have new or worsening respiratory symptoms and are suspected to have developed Grade 2 ILD/pneumonitis related to palbociclib, until ≤ Grade 1, at which time therapy may resume. Palbociclib dose reduction is encouraged in this setting, but is at the discretion of the investigator.

CTCAE v.4.0 Adverse Event	CTCAE v.4.0 Grade	Intervention with Palbociclib
include, but are not limited to, hypoxia, cough and dyspnea)	3, 4	Permanently discontinue palbociclib in patients with ≥ Grade 3 (severe) ILD/pneumonitis. Initiation of systemic therapy for pneumonitis, i.e. steroids, as well as specialty referral to a pulmonary consultant, would be suggested in this setting.

Table 7: *AE triggered Dose Modifications and Treatment Management for Arm A*

9.5. Concomitant Medications

All prior treatment or medication administered during the 30 days prior to randomization and any concomitant therapy administered to the patient throughout the study (with the exception of surgery related medication e.g. anesthetics) until the last visit of the treatment phase to be scheduled 30-42 days after completion of 2 years of therapy, orafter trigger date for early end of treatment phase, must be recorded on the respective page of the eCRF. The generic or trade name of the drug must be specified along with the dose, the duration of treatment, relation to AE and indication for use. During the Follow- Up Phases I and II, limited information on all breast and/or non-breast anti-cancer related therapies must be recorded.

9.5.1. Permitted Ancillary Medications

Supportive care medications are allowed at any time on trial, as long as they are not included in the list of prohibited medications based on CYP induction (see section 9.5.2.1).

Specifically, the following agents are permitted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines
- Bisphosphonates: Patients being treated with bisphosphonates for management of osteoporosis when they enter the study and may continue the medication as long as the dose is stable. Patients may also initiate bisphosphonate therapy while on protocol therapy if it is thought to be medically indicated (with the exception of breast cancer indication; see section 9.5.2.2).
- Rank Ligand Inhibitors
- Agents to assist in management of endocrine therapy-induced side effects (Nonsteroidal anti-inflammatory drugs [NSAIDs], gabapentin, duloxetine, venlafaxine, etc.).

- Diabetes management medication including metformin

Surgery is allowed during protocol therapy, however it is suggested to avoid surgery until the first 12 weeks of protocol therapy have been completed and to avoid nadir of counts at time of surgery. Patients pursuing surgery must hold palbociclib therapy 7 days before the surgery and up to 4 weeks after surgery. Patients undergoing free flap (i.e. Deep Inferior Epigastric Perforator (DIEP) reconstruction) breast reconstruction may hold palbociclib up to 5 weeks after surgery. Patients may resume palbociclib therapy once satisfactory wound healing and recovery have occurred. Patients should continue endocrine therapy if palbociclib is held for surgery.

9.5.2. Prohibited Concomitant Medications

Growth factors, including Granulocyte Colony Stimulating Factor (G-CSF), are not allowed on trial (with the exception of situations where a patient becomes clinically and medically unstable due to neutropenia). Growth factors are, in addition, not allowed in the course of elective surgical procedures. The use of concurrent investigational or other antitumor therapies, other than endocrine therapy, is not permitted for study patients. If a subject must take one of the following medications during the study, and there is no alternative, the subject needs to discontinue palbociclib.

9.5.2.1. CYP3A Inhibitors/Inducers

Potent (Strong/Moderate) CYP3A inhibitors/inducers: Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are potent CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of the following compounds is not allowed in the study:

- Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort.
- Strong CYP3A inhibitors, including, boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.
- Moderate CYP3A inhibitors including amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, verapamil.
- Moderate CYP3A inducers including felbamate, nevirapine, phenobarbital, rifabutin.

9.5.2.2. Anticancer Therapies

No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than those allowed in the protocol will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product label are not permitted during Treatment Phase of the study.

Radiation therapy is not allowed during the active treatment phase of the study.

9.5.2.3. Hormone replacement therapy, hormonal stimulation of the ovaries (i.e. oocyte cryopreservation, IVF or ICSI), topical estrogens (but not intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators e.g. raloxifene, with the exception of tamoxifen are prohibited during the active treatment phase with IP and/or Non-IP.

9.5.3. Medications Not Recommended

The following treatments are not recommended throughout the duration of the Treatment Phase. Alternative therapies should be considered whenever possible:

- The concurrent use of dexamethasone is not recommended.
- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- The use of herbal medicine is not recommended during the Treatment Phase.
- CYP3A Substrates with a Narrow Therapeutic Index: The dose of the sensitive CYP3A4 substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced when given concurrently with palbociclib as palbociclib may increase their exposure.

10. End of Treatment/End of Study Visits

10.1. End of Treatment

Total duration of IP treatment (palbociclib, Arm A) is expected to be approximately 2 years, beginning up to 7 days from the date of randomization (i.e., Treatment Phase). Unless a patient discontinues treatment early or experiences treatment delays, this would result in 26 cycles of treatment administered to the patient. Any premature,

permanent termination of IP treatment is referred to as "Early End of IP-treatment". "End of IP treatment per protocol" means the IP treatment termination after 2 years(refer to 6.1.2) of palbociclib treatment, post randomization. Section 6.1 describes the phase into which the patient will proceed, after permanently discontinuing IPtreatment.

Any one of the following criteria will be reason to stop IP-treatment before 2 years:

- Development of an iDFS event by clinical and/or pathological evaluation. Pathological confirmation of iDFS events is strongly recommended.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator (Endocrine treatment may continue; the decision is at the discretion of the investigator).
- Unacceptable toxicity of, or unacceptable adherence to, either palbociclib or endocrine therapy. Patients who have unacceptable toxicity from palbociclib should continue endocrine therapy wherever possible. Patients, who have unacceptable toxicity to endocrine therapy, necessitating discontinuation of endocrine therapy, must also discontinue palbociclib.
- Patient withdraws consent
- If patient becomes pregnant.

Patients who permanently discontinue IP treatment AND discontinue Non-IP treatment for non-iDFS event reasons will be followed according to Follow-Up Phase I (see section 6.1.2) and the Schedule of Assessments (section 7).

'Early End of Non-IP Treatment' means permanent discontinuation of Non-IP Treatment at any time prior to completion of 5 years standard endocrine therapy (i.e. considering possible standard endocrine treatment up to 6 month prior randomisation this means any discontinuation between 4,5 years and 5 years after randomisation).

'End of Non-IP Treatment, per protocol' means permanent discontinuation of Non-IP Treatment at any time after at least 5 years of standard endocrine therapy.

Following the results of the second Interim Analysis, the IDMC recommended on May 26th, 2020 to prematurely end the Treatment Phase of the PALLAS trial due to futility ofthe analysed data, while no new safety concerns were observed that influenced that recommendation. The SC thereafter decided on May 29th, 2020 that all active PALLAS patients are to discontinue IP treatment and are to be moved to the Follow-Up Phase of the study. The Follow-Up Phase, including visit and assessment schedule, is to be conducted as defined by the study protocol.

10.2. End of Study

10.2.1. End of Study Visit

Patient's end of study visit is the last formal study visit (including Follow-Up Phases I and II), or last formal contact or an unscheduled study visit in case of early withdrawal from all Phases of the study for treatment and follow-up. This coincides with the end of the Follow-Up Phase II (see Section 6.1.4).

10.2.2. End of Study

End of study is the date when the last patient has completed their end of study visit, all data have been collected, and all queries have been resolved.

10.2.3. Managing Randomized Patients Who Never Received Protocol Treatment

Patients who are randomized to the trial but never receive study treatment will be followed for efficacy endpoints (see section 6.1).

10.2.4. Patients Lost to Follow Up

During the duration of the study, sites will be expected to continue efforts to contact all randomized patients as well as regularly consult publicly available information to ascertain vital status of the patient if permissible per local regulation. In cases, where sites cannot successfully contact a patient and is not able to receive appropriate publicly available information for greater than two years (calculated from the last contact), the patient will be noted as lost to follow up.

11. Safety Instructions and Guidance

Palbociclib is currently approved in the US and other countries for metastatic breast cancer and is currently in clinical development. Therefore, the entire safety profile is not known at this time and human experience is currently limited. Currently available information is based on results from ongoing clinical studies. The following safety instructions and guidance for this study is designed to ensure patient safety and will include specific eligibility criteria, safety reporting obligations and monitoring assessments as detailed below.

11.1. Adverse Events – General Overview

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

a. Any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

b. Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 11.5.1.
c. Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
d. Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms requires additional diagnostic testing or medical/surgical intervention, leads to a change in study treatment or concomitant treatment or discontinuation from study drug or is considered to be an AE by the Investigator.
e. Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment.

The investigator is responsible for ensuring that all adverse events (as defined above) are recorded on the respective Adverse Event eCRF page (Rave for US sites or MACRO for Non-US sites) and additionally reported to the respective safety departments (AFT for US sites or ABCSG for Non-US sites) in case the AE fulfills the criteria for expedited reporting in accordance with instructions provided in this section and in Section 11.6.
For each adverse event recorded on an Adverse Event eCRF page, the investigator will make an assessment of seriousness (see Section 11.6.2 for seriousness criteria), severity (see section 11.3), and causality (see Section 11.4).

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by applicable regulations. Adverse events must be described and graded using the terminology and grading categories as defined by NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

11.2. Adverse Events – Reporting Period

Adverse event (Safety) reporting is mandatory from the date of informed consent form signature (i.e., screening phase) until the end of safety reporting period (30 to 42 days after completion of 2 years of therapy or after trigger date for early end of treatment phase, see section 10.1). During the Screening Phase, only AEs deemed to be serious (SAEs) **and** related to protocol mandated and not routinely performed procedures have tobe reported.

11.3. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Grade	Severity

1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

Table 8: *Adverse Event Severity Grading Scale*

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 11.6.2 for reporting instructions), per the definition of serious adverse event in Section 11.6.2.

[d] Grade 4 (only if immediately life threatening) and 5 events must be reported as serious adverse events (see Section 11.6 for reporting instructions), per the definition of serious adverse event in Section 11.6.2.

11.4. Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the adverse event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the IP or Non-IP, indicating"yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	Adverse events will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

Table 9: *Adverse Events - Causal Attribution Guidance*

For patients receiving combination therapy, causality will be assessed individually for each of palbociclib and endocrine therapy. Investigator is responsible for reporting side effects of commercially available drugs to regulatory agency.

11.5. Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the schedule of assessments in Section 7. Adverse events will be collected in a cumulative manner, with duration (start and stop) dates and using CTCAE v4.0 Adverse Event Severity Grading Scale.
For this trial, eCRFs are used for routine AE reporting in Rave (US sites) and MACRO (Non-US sites).

Note: All AEs during the defined AE Reporting Period require reporting regardless of causality. Attribution to treatment or other cause should be provided.

11.5.1. Adverse Event Reporting Exceptions

Recurrence or progression of the underlying malignancy is reportable **only** if the patient dies due to disease recurrence or progression within the reporting period. Hospitalization solely due to the recurrence or progression of the underlying malignancy should not be reported as an SAE. Clinical symptoms of recurrence or progression may be reported as AEs if the symptom cannot be determined as exclusively due to the recurrence or progression of the underlying malignancy, or does not fit the expected pattern of recurrence or progression for the disease under study. If there is any uncertainty about an AE being due to the disease under study, it should be reported as an AE or SAE as appropriate.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization without underlying adverse event (e.g. solely for cosmetic surgery or due to patient´s wish)
- Hospitalization for a preexisting condition provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study
  - The patient has not suffered an adverse event
- Hospitalization due solely to progression or recurrence of the underlying cancer
- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care
- Hospitalization for protocol mandated biopsies

11.6. Expedited Adverse Event Reporting

11.6.1. General Information

Certain events require immediate reporting. The investigator must report such events either to the safety department of AFT (US sites) or ABCSG (Non-US sites) immediately.

The following is a list of events that the investigator must report to the respective safety department **within 24 hours** after learning of the event, regardless of the relationship to study drug:

- Serious adverse events
- Abnormal Liver Function Tests reported as Hy's Law
- Pregnancies

The investigator must report new significant follow-up information for these events to the respective safety department immediately (i.e., no more than 24 hours after becoming aware of the information).

New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and/or IRBs/ECs and/or any other parties as locally required and if applicable.

11.6.2. Serious Adverse Events (Immediately Reportable During Treatment Phase)

A Serious Adverse Event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (at least one overnight stay)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., mayjeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Serious Adverse Events have to be reported on the study specific SAE reporting form to the safety department of AFT (US sites) or ABCSG (Non-US sites) and additionally be documented on the eCRF Adverse Event section in Rave (US sites) or MACRO (Non-US sites) during the adverse event reporting period (see section 11.2).

The Serious Adverse Event reporting period starts at the date of informed consent form signature and lasts until 30 to 42 days after completion of 2 years of therapy or after trigger date for early end of treatment phase. This would be approximately 2 years post-randomization, plus an additional 30-42 days. Duringthe Screening Phase, only AEs deemed to be serious (SAEs) and related to protocol mandated and not routinely performed procedures have to be reported. SAEs deemed to be related to IP treatment must be reported throughout both Follow-Up Phases (I and II) as well.

11.6.3. Pregnancies

Pregnancies have to be reported on the study specific pregnancy reporting formto the safety department of AFT (US sites) or ABCSG (Non-US sites), respectively.

All pregnancies reported during the study should be followed until pregnancy outcome.

11.6.4. Abnormal Liver Function Tests reported as Hy´s Law

Investigators must report as a serious adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST (>3 x ULN) in combination with total bilirubin (>2 x ULN)
- Treatment-emergent ALT or AST (>3 x ULN) in combination with clinical jaundice

The finding of an elevated ALT or AST (>3 x ULN) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the safety department of AFT (US sites) or ABCSG (Non-US sites) immediately (i.e., no more than 24 hours after learning of the event) using the study specific SAE reporting way.

11.6.5. Expedited Reporting Procedures US Sites

For reports of Serious Adverse Events, Abnormal Liver Function Tests reported as Hy's Law and pregnancies, investigators should record all case details that canbe gathered immediately (i.e., within 24 hours) within the AFT Safety Management System. In addition, the event should be captured on the Adverse Event eCRF page within the Rave EDC system during the adverse event reporting period (see section 11.2).
All relevant follow-up information should be submitted through the safety management portal as soon as it becomes available.

11.6.6. Expedited Reporting Procedures Non-US Sites

For reports of Serious Adverse Events, Abnormal Liver Function Tests reported as Hy's Law and pregnancies, investigators should record all case details that canbe gathered immediately (i.e. within 24 hours) on the study specific paper Serious Adverse Event reporting form or Pregnancy reporting form and transmit to ABCSG safety department using the study specific reporting way. In addition the serious adverse event information will be captured on the Adverse Event eCRF page in the EDC system MACRO during the adverse event reporting period (see section 11.2).

Relevant follow-up information should be submitted to ABCSG safety department as soon as it becomes available and/or upon request.

11.6.7. Post – Treatment Follow up (Follow-Up Phases I & II)

Following the active safety reporting period, newly occurred serious adverse reactions (SARs) related to palbociclib, have to be documented on the SAE form and have to be submitted to the Sponsor within 24 h after becoming aware of the event. Serious adverse events occurring to a patient after the Treatment Phase has ended (i.e., during the Follow-Up Phases I & II) should be reported to theSponsors if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

11.7. Expected Toxicities

11.7.1. Adverse Event List(s) for Palbociclib

The primary anticipated toxicity of palbociclib is neutropenia. In the phase I, dose-escalation trial of palbociclib alone in advanced cancers[43], neutropenia was the only dose-limiting toxicity (DLT). Grade 3 neutropenia during cycle 1 was observed in 3/22 patients receiving palbociclib 125 mg PO daily, with no grade 4 neutropenic events observed. Based on this result, 125 mg PO daily became the recommended phase 2 dose (RP2D). Other hematologic AEs of grade 3 or greater during cycle 1 were anemia and leukopenia, occurring in 1 and 4 of 41 patients, respectively. The most common non- hematologic AEs of grade 3 or greater during cycle 1 were fatigue, nausea, and abdominal pain (each occurring in 2 of 41 patients). Of note, there were no complicated hematologic AEs documented, and all hematologic AEs resolved during the off-drug period of a 3 week on/1 week off schedule, and were non-cumulative.

In a phase II trial of palbociclib alone for advanced breast cancer, the only toxicities $\geq$ grade 3 observed were transient neutropenia (50%) and thrombocytopenia (21%)[35]. In a phase II trial of palbociclib plus letrozole for first-line therapy of hormone receptor positive breast cancer, the most common AEs reported were neutropenia, leukopenia, and fatigue[37,45]. The median time to first treatment delay for neutropenia was 58 days, and the median duration of treatment delay until recovery was 5 days (range 1-16 days, Pfizer internal data). In general, hematologic abnormalities were adequately managed with standard supportive care, were not complicated, and resolved during the drug hold with no cumulative toxicity noted.

The Single Reference Safety Document for Palbociclib is the Investigator's Brochure for the compound. Reference safety information can be found in section 7.8 of this document.

11.7.2. Adverse Event List(s) for Commercial Agent(s) – AIs (letrozole, anastrozole, exemestane), LHRH Agonist and Tamoxifen

The most common adverse events experienced with use of AIs include hot flashes, arthralgias, and gradual loss of bone density. The most common adverse events

experienced with use of tamoxifen include hot flashes, night sweats, and vaginal discharge. Venous thromboembolic disease and endometrial cancer are rare risks of tamoxifen.

For detailed description of AEs of the 3 AIs, LHRH Agonist and tamoxifen should be obtained from the particular package inserts (SmPCs) of the locally obtained commercial supplies.

11.8. SUSAR Reporting

Expected adverse reactions and related serious adverse reactions to palbociclib are listed in the Investigator Brochure (IB). All serious unexpected adverseevents judged by either the investigator or the sponsor (AFT for US sites and ABCSG for Non-US sites) will be reported in accordance with applicable local regulations.

12. Measurement of Effect

Disease will be monitored according to ASCO-guidelines[63] and is further detailed in section 7.0 and Appendix B. Data for all types of oncological events will be captured for this study and histologic confirmation of diagnosis is strongly recommended. Biospecimens should be collected at the time of recurrence (see sections 7.0 and 8.2.1). In particular, tumor samples of local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers are desired,if obtainable (see section 8). Patients who discontinue study treatment for any reason should continue to pursue disease monitoring according to ASCO guidelines (see sections 6 and 7) up toa maximum of 10 years after randomization. After the occurrence of an iDFS event, patients should continue in Follow-Up Phase II (ref. section 6.1.2 to 6.1.4).

Following the last visit within the Treatment Phase (section 6.1.2. to 6.1.4 and 10.1), survival and disease status will be collected in all patients during Follow-Up Phase I every 6 months (alternating between annually, in person, with clinical staff and half yearly updates by telephone follow up) until year 5 after randomization. During Follow-Up Phase II survival update and disease monitoring will be performed annually by in-patient visits or telephone contacts with the patient or the provider until a maximum of 10 years after randomization. Imaging tests should be performed according to ASCO guidelines for follow up care. Information will be collected on date and site of non-invasive local recurrence (DCIS), invasive local recurrence, contralateral DCIS, contralateral invasive breast recurrence and, regional recurrence as well as distant recurrence. Limited information will be collected on any breast and/or non-breast anti-cancer related therapies as well as date and cause of deaths and date and diagnosis of secondarymalignancies.

The diagnosis of each type of oncologic event can be made only when the cytological, histological or radiological evidence of disease is confirmed as defined below. For all confirmed oncologic events, the time to event will be based on the earliest date of diagnostic evidence. Initial diagnosis of the event should not be a first occurrence of symptoms, but must be based ona clinical assessment with objective findings, whether by physical exam or radiological determination that is subsequently confirmed as described below. The date of “clinical diagnosis

of an oncological event" will be accepted if it has a close temporal relationship (less than 6 months) to further actions taken in order to achieve definite confirmation of event (i.e. radiologic imaging, cytological or histopathological confirmation) or in order to treat the oncological event. In case more than 6 months elapse between clinical diagnosis and confirmation (as described below), adjudication by a medical reviewer has to be performed.

The following definitions are being used for confirmation of oncological events:

Local recurrence
Local recurrence is defined as the cytological or histological evidence of invasive breast cancer in the ipsilateral breast, or chest wall.

Regional recurrence
Regional recurrence is defined as the cytological or histological and/or radiological evidence of disease in the ipsilateral internal mammary, ipsilateral supraclavicular, ipsilateral infraclavicular and/or ipsilateral axillary nodes or soft tissue of the ipsilateral axilla.

Distant recurrence
Distant recurrence is defined as the cytological, histological and/or radiological evidence of disease recurrence in locations other than local or regional metastasis, for example the subcutaneous tissue, lymph nodes (not regional), lung, bone marrow, liver metastasis, etc.

Second primary invasive breast cancer
Second primary invasive breast cancer is defined as the histological evidence of invasive breast cancer in the contralateral breast, or chest wall.

Second primary invasive cancer (non-breast)
Second primary invasive cancer (non-breast) is defined as the cytological, histological and/or radiological evidence of any second primary invasive cancer of non-breast origin other than any new in situ carcinomas of any site or non-metastatic non- melanomatous skin cancers.

Ductal carcinoma in situ ipsilateral breast
Any histological evidence of ductal in situ carcinoma of the ipsilateral breast.

Ductal carcinoma in situ contralateral breast
Any histological evidence of ductal in situ carcinoma of the contralateral breast.

13. Statistical Considerations and Methodology

13.1. Overview of the Study Design

This is a two arm Phase III study in patients with histologically confirmed HR-positive/HER2-negative early breast cancer (EBC). The primary objective is to compare

invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment (Arm A) versus at least 5 years endocrine therapy alone (Arm B). Patients will be randomized between Arm A and Arm B with equal allocation (1:1) within strata defined by: Anatomic stage (IIA vs IIB/III), assessed by pathologic staging, or by clinical staging if pre-operative therapy was given with the higher stage determining eligibility, Neo/adjuvant chemotherapy (yes vs no), Age (≤ 50vs > 50 years) and Geographic region (North America versus Europe versus Other).

The revised target accrual is 5600 patients, with a maximum of 1000 Stage IIA patients enrolled. Two interim analyses are planned to allow for early stopping due to futility (1st and 2nd) and superiority (2nd only). Potential sample size re-estimation at the first and second interim analyses will be based on the Cui, Hung and Wang[61] method. Sample size and study operating characteristics were computed using East version v5.4.2 (Cytel Inc, Cambridge MA).

13.2. Endpoints

Primary Endpoint: The primary endpoint is invasive disease-free survival (iDFS) using STEEP criteria[62] defined as the time from randomization to the date of the first event: local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, second primary invasive* cancer of non-breast origin or death from any cause. Surviving patients who are event-free will be censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first.

*Second non-breast primary cancers also include e.g. leukemia, myelodysplasia, plasmocytoma but do not include any new in situ carcinomas of any site or non- metastatic non-melanomatous skin cancers.

Secondary Endpoints:

Invasive disease-free survival (iDFS) excluding second primary invasive cancers of non-breast origin defined as the time from randomization to the date of the first event: local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause. Second primary invasive cancers of non-breast origin will not be considered as events for this endpoint. Surviving patients who are event-free will be censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first.

Overall survival (OS), defined as the time period between randomization and death. Surviving patients classified as lost-to-follow up or having withdrawn consent to be followed will be censored at their date of last contact or withdrawal of consent to be followed, whichever occurs first.

Locoregional recurrences-free survival (LRRFS), defined as the time from randomization to the date of the first event: local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer, or death from any cause. Patients with second

primary invasive cancers of non-breast origin or distant recurrence will be censored at the date of diagnosis. Surviving patients who are event-free will be censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first.

Distant recurrence free survival (DRFS) is defined according to STEEP[62] criteria as the time from randomization to the date of the first event: distant recurrence or death from any cause. Patients with a locoregional recurrence will continue to be followed for DRFS. Surviving patients who are event-free will be censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first.

Adverse Events will be collected according to the NCI CTCAE version v4.0.

Clinical Science Endpoints: Adherence measured by Drug Diary, Morisky Medication Adherence Scale, Medication Adherence and McHorney Brief Estimator questionnaires in a subset of patients and primary endpoint (iDFS) effected by baseline body mass index (BMI). See separate document(s) for details regarding clinical science endpoints.

PRO Endpoint: Average score for pre-specified PRO scales over the pre-specified time points during the initial 2-year treatment phase, adjusting for the baseline score. See separate document(s) for details regarding PRO endpoints.

13.3. Analysis Populations

ITT Population: We will use intention to treat (ITT) principles to define the population used for the analysis of the primary endpoint and secondary efficacy endpoints. The ITT Population is comprised of all randomized patients, including those who do not start palbociclib or endocrine treatment. This population provides the basis for the mainefficacy analyses. Patients will be analyzed according to the treatment group to which they were randomized. Randomized patients consist of all patients who have given their written informed consent and for whom there is confirmation of successful allocation of a randomization number through the IxRS (Interactive Voice and Web Response System).

Safety Population (SP): For the purposes of evaluating and monitoring Adverse Events and all other patient safety, the Safety Population (SP) is defined as all randomized patients, excluding those who do not start palbociclib or endocrine treatment, i.e. as- treated. Patients will be analyzed according to treatment actually received. Randomized patients for whom it is unclear whether they took the palbociclib or endocrine treatment will be included in the safety population as randomized.

13.4. Analysis Plans for the Primary Endpoint

The primary analysis of the study will be the comparison of iDFS between Arm A and Arm B using stratified logrank test and group sequential methods to control the overall one-sided Type I error rate at 0.025. Stratified log-rank test will use the following subset of factors used in randomization: Neo/adjuvant chemotherapy (yes vs no), Age (≤ 50 vs >50 years).

The null and alternative hypotheses to be tested are defined using the hazard ratio (HR) of Arm A to Arm B as:

H0: HR ≥ 1
H1: HR < 1

In addition to stratified log-rank test, survival functions will also be summarized using the Kaplan-Meier method according to randomized treatment assignment, and multivariable Cox proportional hazard model with study stratification factors and other known prognostic factors for EBC.

13.4.1. Interim Analysis Decision Rules

Two interim efficacy analyses are planned for monitoring for futility and superiority, and are scheduled to occur when 33% and 67% of the total number of iDFS events are observed.

The first interim analysis will take place after the first 157 iDFS events have occurred and the second interim analysis will take place after accrual has completed and 313 iDFS events have occurred. Under original assumption: It is estimated that the 1st interim analysis will occur < 3 years and the 2nd interim analysis will occur <4 years after the first patient is randomized. Under revised assumptions: the 1st interim analysis is expected to occur <4 years and the 2nd interim analysis to occur <5 years after the first patient is randomized.

The objective of the first interim efficacy analysis will be:

- To assess safety.
- To allow for early stopping of the trial due to futility.
- To consider re-estimation of total sample size.

The objective of the second interim efficacy analysis will be:

- To assess safety.
- To allow for early stopping of the trial due to futility.
- To allow for early stopping of the trial due to overwhelming efficacy (superiority stopping boundary is crossed).
- To consider re-estimation of total sample size.

Although stopping the trial for overwhelming efficacy (superiority stopping boundary is crossed) is not considered as one of the objectives at the first interim analysis, the nominal alpha for the first interim analysis is still taken into account when calculating overall type I error.

The following table summarizes the nominal significance level, corresponding hazard ratio, and 3-year and 5-year iDFS rates for each arm at the 2nd interim analysis and the final analysis when 67% of total events (313 events) or 100% of total events (469 events) are observed. The corresponding hazard ratio is estimated

under the assumption of proportional hazards, and the corresponding 3-year / 5- year iDFS rates are estimated under the assumption of exponential distribution for iDFS.

Analysis	Nominal α level (1-sided)	Estimated Hazard ratio	Estimated 3-year iDFS rate for		Estimated 5-year iDFS rate for	
			Control arm	Palbociclib arm	Control arm	Palbociclib arm
Original assumptions *:						
2nd interim analysis	0.006	0.753	0.881	0.909	0.81	0.853
Final analysis	0.0231	0.832	0.881	0. 900	0.81	0.839
Revised assumptions *:						
2nd interim analysis	0.006	0.753	0.897	0.923	0.835	0.876
Final analysis	0.0231	0.832	0.897	0.915	0.835	0.863

* Original and revised assumptions given in 13.5.1

At each interim efficacy analysis, statistical hypothesis tests will be performed only for the primary efficacy endpoint, iDFS and the secondary endpoint, iDFS excluding second primary invasive cancers of non-breast origin. O'Brien – Fleming type stopping boundaries[58] based on the Lan-DeMets spending function will be applied. Futility criteria will not be used to calculate the nominal alphas in order to control the overall Type I error (non-binding method). The Z-statistic from a one-sided, stratified logrank test will be calculated and compared to the stopping boundaries, and are defined on the Z-statistic scale for formal comparison to logrank test. In addition to the boundary and observed Z-statistics, the IDMC will be provided Kaplan-Meier product limit estimators to the survivalfunctions for each arm, and estimated HRs and 95% CIs from the corresponding Cox proportional hazard models for iDFS.

The IDMC will also be provided estimates (Kaplan-Meier, HR and 95% CI) for the secondary endpoint, iDFS excluding second primary invasive cancer of non-breast origin.

See Section 13.9 for further details as to Safety Monitoring and the IDMC.

Decision rules for sample size re-estimation at the first and second interim analyses will be based on the Cui, Hung and Wang[61] method using conditional power based on the point estimate and standard error for the HR. Details on the sample size re-estimation and modifications to the stratified log-rank test to control the overall Type I error will be provided in the Statistical Analysis Plan (SAP).

13.4.2. Final Analysis Decision Rules

The primary analysis of iDFS will occur when 469 iDFS events are observed if no changes are made based on sample size re-estimation during interim analyses.

In that case, results of the hypothesis test will be based on the Z-statistic and p-value from the stratified logrank test in the ITT population.

The actual nominal α levels for the interim analyses and for the final analysis will depend on the fraction of total events occurred at the time of interim analysis, and at final analysis is noted to be 0.0231 (one-sided) under exact equal spacing in information time.

	First Interim	Second Interim	Final Analysis
iDFS Events (%)	157 (33%)	313 (67%)	469 (100%)
Expected number of patients accrued (under H1 and original assumptions **)	3996	4600	4600
Approximate time after study Activation (under H1 and original assumptions **)	32 months	45 months	58 months
Expected number of patients accrued (under H1 and revised assumptions) **	5235	5600	5600
Approximate time after study Activation (under H1 and revised assumptions) **	39 months	52 months	65 months
Superiority Bound: critical Z	3.710 *	2.511	1.993
Nominal Alpha	0.0001	0.0060	0.0231
Accumulated Alpha	0.0001	0.0061	0.0250

* Stopping for superiority is not considered in the 1st interim.
** Original and revised assumptions given in 13.5.1

13.4.3. A pre-defined iDFS event rate in Stage IIA breast cancer patients of the control arm

Considering that the iDFS event rate for Stage IIA breast cancer patients may be lower than in the other patient segments in this trial, it may be required to pre-define an event rate that must be observed in Stage IIA breast cancer patients of the control arm in order to make a reliable estimate of the treatment effect in this subgroup of patients.

There were 2 registrational trials comprised of patients with Stage IIA breast cancer. In the ATAC trial (2002)[59], the disease free survival (DFS) event rate was 10% for anastrozole arm and 12% for tamoxifen arm. In the BIG 1-98 trial (2005)[60], the DFS event rate was 8.8% for letrozole arm and 11% for tamoxifen arm. The DFS event rate in Stage IIA breast cancer patients observed in PALLAS could be lower than the event rate observed in these two trials. It is therefore assumed that an 8% iDFS event rate in Stage IIA breast cancer patients

of the control arm in the PALLAS study can be considered acceptable in order to reliably estimate the treatment effect.

13.4.4. Update Analysis for Stage IIA breast cancer patients

An update analysis will be conducted after 8% iDFS event rate in Stage IIA breast cancer patients of the control arm is observed.

The update analysis is a subgroup analysis for Stage IIA breast cancer patients to estimate treatment effect on iDFS. The purpose of the update analysis is to make a reliable estimate of the treatment effect on iDFS with sufficient number of events in Stage IIA breast cancer patients. There will be no hypothesis testing in the update analysis.

Assuming that 1000 Stage IIA breast cancer patients will be enrolled within 1 year of study start, it is estimated that the update analysis, if needed, will occur around 6.3 years after study start and 1.5 years after the final analysis.

13.4.5. Analysis at End of Study

At End of Study, exploratory analyses of the secondary time-to-event endpoint OS, as well as other endpoints as requested will be conducted.

13.4.6. Impact of COVID-19 Pandemic

If, due to the COVID-19 pandemic, it becomes apparent that additional sensitivity analyses are necessary, specific statistical analyses will be documented in the statistical analysis plan (SAP) or additional documents.

13.5. Sample Size, Accrual time, and Study Duration

13.5.1. Sample Size

The revised total accrual is 5600 patients. A maximum of 1000 Stage IIA patients are to be enrolled. If the maximum is reached, the study will proceed to enroll only Stage IIB and III patients.

Sample size is based on a target effect size on the hazard ratio (HR) scale for Arm A over Arm B of 0.75 as a clinically relevant level of improvement in iDFS. To have 85% power to detect this difference after accounting for interim analysis plans, the final analysis will occur when 469 iDFS events are observed.

Original assumptions:
Total accrual is determined based on the assumed iDFS for patients on Arm B (control) using results from ECOG 5103: Phase 3 randomized study of adjuvant therapy comprising doxorubicin hydrochloride, cyclophosphamide, and paclitaxel with versus without bevacizumab in patients with lymph node-positive or high-risk, lymph node-negative breast cancer.[48] In the ER+ subset, the 5-year iDFS rate was 0.74, 0.82, and 0.92 for Stages III, IIB, and IIA, respectively. By simulation, it is anticipated that the 5-year iDFS rate will be 0.81 in Arm B for a mixed patient population with 39% Stages III, 39% IIB and 22% IIA patients (capped). The alternative hypothesis is a 25% risk reduction with Arm A which equates to a 5-year iDFS rate of 0.854 (absolute difference of 4.4%).

To define the total sample size, it is assumed that time to iDFS event and time to dropout follow an exponential distribution. The dropout rate is assumed to be 10% at 5 years. Assuming a quarterly step-wise increase in enrollment over the first year, and a constant rate of 153 patients per month thereafter, 4600 patients will be enrolled within 36 months. The final analysis at 469 iDFS events is anticipated to occur after 22 months of additional follow-up.

Revised assumptions:
The first patient was randomized in September 2015, and enrollment reached the cap of 1000 Stage IIA patients in September 2017 and closed to further accrual of this patient cohort. As of February 2018, over 3500 patients have been enrolled into the study, with the rate of recruitment exceeding 250 during January 2018. The recruitment period is therefore anticipated to be shorter than originally projected. Further, contemporary trials investigating adjuvant treatment of hormone receptor-positive breast cancer have shown improved clinical outcomes and lower event rates. Specifically, in NSABP B-47 the 5-year iDFS rate was 0.896 and 0.892 with and without the addition of trastuzumab to standard adjuvant therapy, respectively. In ABCSG-18, a randomized placebo-controlled study of the addition of denosumab to standard adjuvant AI therapy (n = 3425), the 5-year iDFS rate was 0.78, 0.85, and 0.89 for Stages III, IIB, and IIA, respectively. In TEXT, premenopausal women received ovarian functionsuppression with anti-estrogen therapy and 5-year iDFS rate was 0.77, 0.87, and
0.92 for Stages III, IIB, and IIA, respectively. Under an exponential model, the hazard ratio of iDFS in TEXT relative to the control arm of ECOG 5103 is 1.15, 1.42 and 1.0 for Stages III, IIB, and IIA, respectively, and supports an additional 1000 patients that are stage III or IIB, such that the study population is expected to be 41% Stages III, 41% IIB and 18% IIA patients (capped at 1000 patients).

A revised total sample size of 5600 is anticipated to be enrolled within 41months. By simulation using (a) the actual accrual through 2017 and constant accrual thereafter, (b) the 5-year iDFS rates for stage IIB and III observed in TEXT, and (c) the original dropout rate of 10% at 5 years, the final analysis at 469 iDFS events is anticipated to occur after 24 months of additional follow-up (65 months total).

Power is also calculated for the secondary endpoint: iDFS excluding second primary invasive cancers of non-breast origin as an event. Under the assumption that 12% of iDFS events will be second primary invasive cancers of non-breast origin, and time to event for this endpoint will follow an exponential distribution, there will be a 79.3% power to detect a HR = 0.75 for the secondary endpoint of iDFS excluding second primary invasive cancers of non-breast origin using a one-sided alpha = 0.025.

The expected study duration to primary analysis of iDFS is 5.4 years.

Power is also calculated for the secondary endpoint: Invasive disease-free survival (iDFS) excluding second primary invasive cancers of non-breast originas an event. Under the assumption that 12% of iDFS events will be second primary invasive cancers of non-breast origin, and time to event for this endpoint will follow an exponential distribution, there will be 79.3% power to detect a HR = 0.75 for the secondary endpoint of iDFS excluding second primary invasive cancers of non-breast origin using a one-sided alpha = 0.025.

The expected study duration to primary analysis of iDFS is 5.4 years.

13.5.2. Accrual Rate and Accrual Duration

Under original assumptions: Accrual is expected to reach a rate of approximately 153 patients per month after the first year of enrollment and have a total duration of 36 months. Enrollment will not be suspended for interim analysis. With quarterly step-wise increases to the maximum rate over the first year of enrollment, the target sample size is 4600 patients.

It is also assumed that the cap of 1000 Stage IIA breast cancer patients will be reached within 1 year of study start.

A revised total sample size of 5600 is anticipated to be enrolled within 41months.

13.5.3. Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study will be the date of awareness of the 469th event and is expected to occur at least 5 years from the first patient randomized.

13.6. Study Operating Characteristics

Under the interim and final analysis plan for efficacy and futility, there will be 85% power to detect the target HR = 0.75 in the comparison of Arm A to Arm B without consideration of sample size re-estimation. The following table provides

the probabilities of declaring the experimental intervention to be superior under other effect sizes.

Hazard ratio (Arm A to B)	Power
0.700	96.0%
0.725	91.7%
0.750	85.0%
0.775	75.6%
0.800	64.1%

13.7. Analysis Plans for Secondary, Translational and PRO Endpoints

For the time-to-event efficacy endpoints (iDFS excluding second primary invasive cancers of non-breast origin, DRFS, LRRFS and OS), analyses will be done comparing Arm A vs Arm B. In addition to stratified log-rank test, survival functions will also be summarized using the Kaplan-Meier method according to randomized treatment assignment. Multivariable Cox proportional hazard model with study stratification factorsand known prognostic factors for EBC will be used to calculate adjusted hazard ratios and95% confidence intervals.

Toxicities will be summarized by maximum grade for all-causality adverse events (AEs) during protocol treatment. Serious adverse events (SAEs) will be analyzed using the previously defined safety population. Rates will be reported with 95% binomial exact confidence intervals. Actual laboratory values (vs. CTCAE grades) may additionally be summarized using graphical techniques, and summary statistics (e.g., means, median, standard deviations, ranges).

All statistical inferences for secondary efficacy and patient safety will use two-sided alpha = 0.05.

Further analysis details will be described in the statistical analysis plan (SAP). Details including how to evaluate iDFS and OS in genomically defined breast cancer subgroups based on a pre-specified genomic assay and how to compare quality of life by treatment arm through patient reported outcomes as well as adherence in a subgroup of patients, etc. will be described in a separate SAP.

13.8. Correlative Science Objectives (TRANS-PALLAS)

The Statistical Analysis Plan for all correlative science objectives (also known as "TRANS-PALLAS") will be contained within a separate document. Of note, the Primary Translational Objective will not be considered in controlling the family-wise error rate of the primary and secondary clinical objectives of the study.

13.9. Independent Data Safety Monitoring the Study

Interim monitoring of data and safety will be reported to an Independent Data Monitoring Committee (IDMC). IDMC will review the safety data on at least a semi-annual basis, in conjunction with the results of any interim and final analyses and come up with recommendations to the SC in special consideration of any identified potential safety risks. Based on the recommendations of the IDMC, the SC will decide to either, proceed with the trial as planned, amend the protocol accordingly or prematurely terminate the trial. Once all patients are in follow-up, no further IDMC meetings take place.

A preplanned safety analysis will occur when the first patient enrolled has completed one year of protocol therapy,and is estimated to occur when approximately 1/3 of patients are enrolled to the study. In addition to the data from the PALLAS study, the IDMC will also evaluate the safety data available in the Pfizer safety data base from ongoing or completed studies of palbociclib and endocrine therapy in the adjuvant and MBC (metastatic breast cancer) settings, with a goal to assess safety of the combination of palbociclib and endocrine therapy, as well as confirm the appropriateness to continue the treatment into the second year of palbociclib exposure.

14. Correlative Sciences and Clinical Data Science

Described protocol objectives as well as future research proposals can be generally categorized into projects requiring access to study data only versus requiring access to study data and surplus samples.
´Clinical Study Data Projects´ (not involving (surplus) study samples) may be reviewed separately from ´Translational Research Projects´ (involving study data and (surplus) study samples and handled by TRANS-PALLAS working groups and TRC, as defined in respective charters).
´Adherence/PRO´ research (requiring access to specific study data only) may be viewed as a further sub-group of ´Clinical Study Data Projects´.
Multiple tissue- and liquid-based translational research studies are scheduled throughout the course of the PALLAS trial to evaluate potential markers of response and/or resistance in patientsreceiving endocrine therapy with palbociclib versus endocrine therapy alone. The companion TRANS-PALLAS Investigator Manual of Procedures will be developed by the TRANS-PALLASscientific steering committee.
Additionally, examination of patient-reported outcomes (PRO)/quality of life in a sub-group of patients as well as adherence to oral therapy, and interaction of metabolic state and response to palbociclib will occur.
Clinical Data Projects will be based on scientific research proposals brought to the attention of the study leadership after the primary analysis.
Detailed analyses will be described in separate document(s).

15. General Regulatory Considerations and Credentialing

15.1. Regulatory and ethical compliance

By signing the Protocol, the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his personnel as well as the IRB/IEC. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT/ABCSG will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT/ABCSG or Pfizer must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

15.2. Ethics and Good Clinical Practice

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

Studies conducted in the European Union/European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC including 2005/28/EC) until the E.U. Directive 2001/20/EC will be repealed and the E.U. regulation 536/2014 will enter into force by the publication of E.U. or EMA.

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

15.3. Confidentiality

Patient medical information both, associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will in generally not be provided to study investigators unless a request for research use is granted. The overall results of any

research conducted using biologic specimens will be available in accordance with the effective Translational Research Committee policy on study data publication.

15.4. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendmentto the protocol. Such amendment will be released by AFT/ABCSG, agreed by the investigator(s) and approved by relevant IRBs/IECs and health authorities according to local requirements prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs/IECs and/or health authorities must be provided to AFT/ABCSG before the study is initiated.
Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes willbe released by the AFT/ABCSG, agreed by the investigator(s) and notified to the IRB/IEC(s) and/or health authorities according to local requirements.
Each change in the protocol should be reported to Pfizer who supplies the Investigational Product prior to submission to the involved IRB/IEC(s) and/or health authorities.

15.5. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patients and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Furthermore, it is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed Informed Consent Form must accomplish with the ICH GCP guideline and regulatory requirements.
The eCRF for this study contains a section for documenting patient's Informed Consent(s), and this must be completed appropriately.

If new palbociclib safety information results in significant changes in the risk/benefit assessment, the Informed Consent Form should be reviewed and updated if necessary. All patients who may be directly affected (including those already being treated) should be informed of the new information, given a revised form and give their consent to continue in the study.

15.6. Financial Disclosure

Investigators will provide the respective study Sponsor with adequate and accurate financial information in accordance with local regulations and laws in order to allow the Sponsor to submit complete and accurate financial certification or disclosure statementsto the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

15.7. Quality Control

The study will be monitored according to GCP by regular site visits and calls. The responsible and adequately trained monitor (Clinical Research Associate, CRA) or his/her designee will contact and visit the study sites as defined in the study specific Monitoring Plan. The monitor will be permitted to inspect the various records of thestudy patients (e.g. source documents) on request provided that the patient confidentialityis maintained in accordance with local regulations.
The monitor is responsible for eCRF inspection on a regular basis throughout the study according to the study specific Monitoring Plan in order to verify adherence to the study protocol and in order to verify completeness, consistency and accuracy of the entered data. Furthermore, the monitor follows the progress of patient enrollment and ensures thatIP is stored, dispensed and accounted for according to defined specifications. The monitor will access laboratory test reports and other patient records needed for verification of eCRF entries. The investigator or his/her designee agrees to cooperatewith the monitor to ensure resolution of problems and other issues identified during studymonitoring.

Details will be outlined in the study specific Monitoring Plan.
The investigational site must also allow inspections by applicable health authorities and audits by the respective study Sponsor.

15.8. Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to the respective Sponsor and if locally applicable, to the respective IRB/EC in accordance with local IRB/EC policies andprocedures. Specific procedures and reporting requirements for the PALLAS study are defined in the common Protocol Deviation Management Plan for the study.

For COVID-19 related measures implemented for recording and defining protocol deviations, please refer to 6.10.

15.9. Retention of Records

Any records and documents relating to the conduct of this study and the distribution of IP, including ICFs, eCRFs, PRO data, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for a minimum of 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

15.10. Trial Administrative Governance Structure

15.10.1. Structure Co-Sponsorship (AFT, ABCSG GmbH)

The PALLAS study is legally governed by two different study Sponsors:

- **Alliance Foundation Trials (AFT), LLC** is the official and legal Sponsor for the area of United States of America and in this function responsible for US-sites, US operations, US regulatory and safety affairs etc.

  US Sites belong to AFT as study Sponsor and will hence have to report to this organization and should follow US instructions and US procedures as described within this protocol and any other study related US guidelines, unless otherwise indicated.
- **Austrian Breast and Colorectal Cancer Study Group (ABCSG GmbH)** is the official and legal Sponsor for all area outside of the United States of America and in this function responsible for Non-US sites, Non-US operations, Non-US regulatory and safety affairs etc.

  Non-US Sites belong to ABCSG as study Sponsor and will hence have to report to this organization and should follow Non-US instructions and Non-US procedures as described within this protocol and any other study related Non-US guidelines, unless otherwise indicated.

  Among the scope of this study, ABCSG collaborates with the Breast International Group (BIG) as co-Lead partners, and with a number of different BIG Groups.

15.10.2. Steering Committee (SC)

The Steering Committee is composed of and working according to the study related SC Charter. The SC is responsible for top-level trial design and management decisions, also in consideration of any IDMC recommendations.

15.10.3. Executive Committee (EC)

The EC is composed of and working according to the study specific EC Charter. It represents a subcommittee of the SC and serves as a rapid decision making body, when necessary.

15.10.4. Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee (IDMC) is composed of and working according to the study specific IDMC Charter. This committee will independently monitor the safety of the patients enrolled into the study as well as data integrity and provide recommendations to the SC.

15.10.5. Translational Research Committee (TRC)

The Translational Research Committee is composed of and working according to the study related TRC charter. This committee will review all research project proposals requesting access to study data, biological samples collected during the conduct of the Study, make recommendations to the Steering Committee (SC) in line with the Policy for Access to Study Data and Biological Samples.

15.10.6. Publication and Presentation Policy

Publications and presentations resulting from the PALLAS trial will comply with recognized ethical standards concerning publications and authorship, including Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors. Furthermore, publications and any kind of presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific policy developed for this study. The detailed “Publication and Presentation Policy” shall be approved by the Study Steering Committee and made available to all investigators, sites andgroups participating in the study.

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17. Appendices

APPENDIX A: Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

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

Please refer to *http://oncologypro.esmo.org/Oncology-in-Practice/Practice-Tools/Performance-Scales* for conversion instructions between Karnofsky Scale and ECOG Status.

APPENDIX B: PALLAS ~ Phases for Data Collection & Follow-Up

The following table contains a quick reference and description of the data collection and follow-up phases for the study. Refer to sections 6, 7, 9, and 10 for full details as to the requirements of data collection and how patients progress through the phases.

	SCREENING	RANDOMIZATION/C1D1 to YEAR 2[a]	YEARS 3-5	YEARS 6-10[c]
Phase	**Screening**	**Treatment Phase**	**Follow-Up Phase I**	**Follow-Up Phase II**
Timing of Assessments or Updates	Variable, specified in Eligibility and Assessment Table.	Visits Required Intensive Data Collection.	Annual visits required in person, with clinical staff. Q6 months Follow Up by Phone calls or in person visits. Intervals based on date of randomization. Move to this phase after regular treatment completion or at the time of Early End of Treatment for non-iDFS event reason.	No in person visits required beyond standard of care, except for the visit at year 7 and at year 10, as here blood samples have to be collectedAnnual phone calls from the site to the patient or provider required. Intervals based on date of randomization. Move to this phase at the time of 1st iDFS event or at the end of Follow-Up I.
Data Collection (Via Case Report Forms, PRO and Adherence Questionnaires, SAE Reports)[b]	Baseline Assessments (e.g. Informed consent, Inclusion & Exclusion, Demographics, Labs, Types of anti-cancer therapy, SAEs related to protocol mandated and not routinely performed procedures, Medical History, Concomitant med…)	Treatment Phase Assessments (e.g. IP Dosing, Dose Modifications, Vital Signs, AEs, SAEs, PROs, Concomitant med, Labs, Drug Diaries, Adherence Questionnaires…)	Follow-Up Assessment (e.g. breast or non-breast anti cancer therapies, SAEs related to IP therapy, PROs and Adherence Questionnaires 36 months post randomization…)	Follow-Up Assessments (e.g. Survival Status, subsequent oncological events (if available), limited information on breast and/or non-breast anti-cancer related therapies and SAEs related to IP therapy…)
Disease Monitoring	Yes	Per ASCO Guidelines.		
Biospecimens	Yes	Yes, according to table 3 Strongly encouraged to obtain samples from local/regional ipsilateral and/or distant recurrences and/or contralateral breast cancers. Specifically, at the year 7 and year 10 visit, there will be additional sample collection (to obtain circulating cfDNA as well as plasma samples)		
Therapy Type		IP Therapy (Arm A)		
	Adjuvant endocrine therapy (Non-IP) allowed < 6 months of randomization.	Non-IP Therapy (Arms A & B)		Non-IP Therapy (Arms A & B)
End of Study Visit		End of Study Visit, per Patient (Past formal study visit, including follow-up)		

a) Plus one final 30-42 day visit beyond the patient's final cycle of IP and/or Non-IP treatment during Treatment Phase (refer to Section 6.1.2).

b) Refer to the Schedule of Assessments (see protocol section 7).

c) Patients will be followed until a maximum of 10 years from randomization.

APPENDIX C: AJCC Cancer Staging from Edge S, Byrd DR, Compton CC, et al. AJCC cancer staging manual (7th ed). New York, NY: Springer; 2010

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M
0	Tis	N0	M0
IA	T1*	N0	M0
IB	T0	N1mi	M0
	T1*	N1mi	M0
IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Notes

* T1 includes T1mi.

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+)
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget`s)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor >1 mm but ≤ 5 mm in greatest dimension
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor >20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules) Note: Invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma (see "Rules for Classification")

Distant Metastases (M)

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Regional Lymph Nodes (N)

Clinical	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

Notes

* "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

Regional Lymph Nodes (N)

Pathologic (PN)*	
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
pN0(i–)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR)**, but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected****, or in ipsilateral supraclavicular lymph nodes.
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of

	one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases of macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Notes

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node", for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

APPENDIX D: Recommendations on adequate local treatment for PALLAS trial candidates

In the PALLAS trial, all study participants are required to have undergone adequate initial local treatment for their breast cancer including surgical resection, with or without radiotherapy. Guidance on the definition of adequately treated patients prior to randomization is provided below:

Positive Sentinel Node

Based on the 2016 ASCO Guidelines on sentinel lymph node biopsy for patients with early-stage breast cancer[96] a patient who has a limited positive sentinel lymph node biopsy and will be receiving adjuvant radiotherapy after breast conservation does not require a completion axillary lymph node dissection (ALND). Such patients are eligible for enrollment onto the PALLAS trial. However, it is strongly recommended that candidates for PALLAS who underwent breast-conserving surgery and had 1-2 sentinel lymph node metastases without ALND subsequently undergo conventionally fractionated whole-breast radiotherapy.

PALLAS candidates who had a mastectomy and positive sentinel lymph node biopsy may have had a completion ALND. If mastectomy was performed and no ALND pursued, adjuvant radiotherapy is strongly recommended.

Surgical Resection Margins

Invasive breast cancer should have been excised to the best of local surgical ability. Patient's surgical treatment is considered complete as long as there is no gross residual disease. The inked margins of breast conservation surgery or mastectomy should ideally be histologically free of invasive breast cancer and ductal carcinoma in situ, with the exception of the posterior margin if this margin is the pectoralis major fascia or the anterior margin if this is the dermis. Patients with resection margins positive for lobular carcinoma in situ are eligible. In patients who undergo a nipple sparing mastectomy (NSM), retro-areolar tissue should have been excised and analyzed intraoperatively. If theretro-areolar margin is positive for DCIS or invasive cancer, the nipple areolar complex (NAC) should be removed.