Informed Consent Form (Version 1.0)

This Informed Consent From is for patients with ER+ /HER2- unresectable locally advanced or metastatic breast cancer with ESR1 mutation who we are inviting to participate in research on FWD1802.

Study Title:	A phase I open-label dose escalation trial of FWD1802 as monotherapy and in combination with Palbociclib in patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer
Protocol Number:	FWD1802-001
Version/Date:	1.0/ February 16, 2023
Investigational Product:	FWD1802
Study Phase:	Phase I
Sponsor:	Shenzhen Forward Pharmaceuticals Co. Ltd
Princeple Investigator	
Contact:	Chenggang Zhu 8618621958197 zhucg@forward-pharm.com

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

You are being invited to volunteer for a medical research study. You must read and sign this form before you agree to take part in this study. This form will give you more information about this study. Before you decide if you want to be in this study, you can talk to anyone you feel comfortable with about the research. After reading this form, please ask the Study Doctor or the staff as many questions as you need to. Do not sign this form if you have any questions that have not been answered.

The Study Doctor (investigator) is being paid by the sponsor, Shenzhen Forward Pharmaceuticals Co. Ltd, to conduct this research study.

You must be honest with the Study Doctor about your health history or you may harm yourself by participating in this study.

Purpose of the Research

The Investigational New Drug (IND) being tested in this study, FWD1802 Tablet, is being developed by Shenzhen Forward Pharmaceuticals Co. Ltd. and is a promising new treatment for ER+ /HER2- unresectable locally advanced or metastatic breast cancer. “Investigational” means that FWD1802 Tablet have not been approved for sale by the FDA, but the FDA has allowed this study to be performed. This study will be the first time FWD1802 Tablet will be given to humans. Extensive testing has been performed and reviewed by the FDA. In this study, the tablet will be taken by mouth with water.

The purpose of this study is:

- To see how safe and how well the body tolerates the FWD1802 tablets (the study drug) / combination with Palbociclib .
- To see how the body absorbs and breaks down the study drug / combination with Palbociclib.
- To see if the study drug acts as expected in the human body;

This information about FWD1802 tablets is determined from people like you, who have ER+ /HER2- unresectable locally advanced or metastatic breast cancer and choose to participate in this study. More details of the study are provided later in this document.

Type of Research Intervention

The first step is to carefully read this document. It provides you with very important information about the study:

- what you need to do if you decide to participate in the study;
- what will and might happen to you;
- when to visit the clinic;

- how your medical information is used;
- and how to contact the study staff.

There is a lot of information in this document. Feel free to share this document with people who are important to you and that you trust. Ask as many questions as you need to make sure you understand what is being asked of you.

Step 2: You will meet with the study staff to talk with you about the study. They will answer your questions. Remember that you are volunteering to particiate in this study, and if you do not feel comfortable, you do not have to participate.

Step 3: If you want to participate in the study and all of your questions have been answered, you will be asked to sign the document.Your signature means that you understand the contents of the document and you want to participate in this study. Ther study staff members who explained and discussed this with you will also sign this form. You will be given a copy of the document that has all signatures.

Step 4: Once you sign this document, you will be considered “enrolled” in the study. Once enrolled, each participant, including yourself, will be called a “subject” while being part of the study. You will be assigned a unique subject number and then be scheduled for reviewing your health history, testing and examination to determine if you can be in the study. You must disclose all past and present diseases, allergies, and all medications that you are taking, including prescription drugs, over-the-counter drugs, vitamins, and herbal supplements.

Step 5: If you qualify for the study, you will be assigned a group, receive additional information, and provided the study drug.

The amount of drug you are given at one time is called a dose. The doses are measured in the strength (5 mg, 25 mg, and 150 mg) and the number of drug tablets. The dose amount, dosing schedule and dose status you end up receiving may be adjusted to something different instead of what is shown below, based on a decision made by the study doctor and sponsor after the safety review of the evolving data during the study.

Participant Selection

Research subjects must meet certain requirements. You have been invited to participate in this research study because you are a ER+/HER2- unresectable locally advanced or metastatic breast cancer patient who has failed or is intolerant in standard treatment, or has no standard therapy.

You cannot be in this study if you are an employee of Shenzhen Forward Pharmaceuticals Co. Ltd., clinical research unit (CRU), or the study site. You cannot be an immediate family member of an employee of the study site; an immediate family member is a spouse, parent, child, or sibling, whether biological or legally adopted.

How many people will take part in this Study?

Approximately 99 subjects will be enrolled in this study.

To be Enrolled in this Study

You must meet all of the following inclusion criteria to be eligible for participation in this study. These criteria will be checked during Screening period.

1. Patients must understand and voluntarily sign the Informed Consent Form (ICF).

2. Patients ≥ 18 years, male or female.

3. Provision of blood sample to test ESR1 mutation status and for other biomarker assessment. In part A/B, the ESR1 mutation status will be tested retrospectively; In part C, only the patients with ESR1 mutation positive are eligible.

4. Documented positive oestrogen receptor status of primary or metastatic tumour tissue, according to the local laboratory parameters. These laboratory parameters are consistent with accepted diagnostic guidelines such as the American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) Clinical Practice Guideline for Pathologists estrogen (ER), progesterone receptor (PgR) and HER-2 negative testing in breast cancer. If possible, ER and HER2 status evaluation should be based on recently obtained Tumor Biopsy samples.

5. Menopausal women according to one of the following criteria:

   - Prior bilateral ovariectomy;

   - Patients ≥ 60 years of age;

   - Patients < 60 years of age presenting an amenorrhea of more than 12 months and follicle stimulating hormone (FSH) and plasma estradiol levels within the postmenopausal range as assessed by the local laboratory in the absence of chemotherapy, tamoxifen, tolimifene, or ovarian castration in the past 1 year, and no oral contraceptives, hormone replacement therapy, or gonadotropin-releasing hormone agonist or antagonist;

   - Patients < 60 years of age who are taking either tamoxifen or tolomifene with two consecutive FSH and estradiol levels in the postmenopausal range;

   - Or premenopausal or perimenopausal female subjects but must be willing to receive and maintain an approved luteinizing hormone-releasing hormone (LHRH) agonist during the study treatment period (LHRH agonist treatment initiated 28 days prior to the first study drug treatment); or for males: willing to receive and maintain an approved LHRH agonist during the study treatment period (LHRH agonist treatment initiated 28 days prior to the first study drug treatment).

6. Previous therapy failed or intolerable, or standard therapy not available: Part A/C: Patients should have received at least 1 line existing therapy (ET), or received no more than 2-line systematic chemotherapy for advanced/metastatic disease, no more than 1 target therapy; Part B: Patients should have received at least 1 line ET, or received no more than 1-line systematic chemotherapy for advanced/metastatic disease, no more than 1 target therapy.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

8. At least one measurable lesion according to RECISTv1.1 criteria.

9. Life expectancy ≥ 12 weeks.

10. Adequate organ and bone marrow function (no use of hematopoietic stimulating factor, no blood transfusion or human albumin within 7 days prior to screening):

    - Hemanalysis: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L; Platelet count (PLT) ≥100×10^9/L; Hemoglobin (HGB) ≥ 90 g/L;

    - Hepatic function: Serum Total bilirubin (TBIL) ≤ 1.5 Upper limit of normal value (ULN); Alanine aminotransferase (ALT) and Aspartate transferase (AST) ≤ 3×ULN in subjects without liver metastasis; ALT and AST≤ 5×ULN with liver metastasis;

    - Renal function: Serum creatinine ≤ 1.5×ULN or estimated creatinine clearance (CLcr) ≥ 50 mL/min as calculated using Cockcroft-Gault formula;

    - Coagulation function: Activated Partial thromboplastin Time (APTT) and international normalized ratio (INR) ≤ 1.5×ULN (or within target range if on anticoagulation therapy);

    - Cardiac function: Echocardiography (ECHO) shows left ventricular ejection fraction (LVEF) > 50%.

11. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose. Female patients of childbearing potential must agree to use effective methods of contraception from the time of signature of informed consent, throughout the study and for 6 months after the last dose of the investigational product, like double barrier methods, condoms, oral or injectable contraceptives, intrauterine devices, etc. All female subjects will be considered to be of childbearing potential unless they are postmenopausal, postmenopausal, or sterilized (hysterectomy, tubal resection).

You **cannot** be enrolled in this study, if you meet any of the following exclusion criteria at screening period and dosing period:

1. Documented medical history or ongoing gastrointestinal disease (Including difficulty in swallowing capsules, Crohn's disease, ulcerative colitis, or short bowel syndrome) or other malabsorption that may affect the absorption of oral study drug.

2. Participated in other clinical trials of investigational drugs or investigational devices within 4 weeks before the first medication; or received chemotherapy, targeted therapy, immunotherapy and clinical trial medication and other anti-tumor treatment within 4 weeks, or received radiotherapy, endocrine drugs or Chinese traditional medicines with anti-tumor indications 2 weeks prior to the first dose.

3. The toxicity of previous anti-tumor treatment has not recovered to grade 0 or 1 (except for alopecia, chemotherapy-induced peripheral neurotoxicity ≤ grade 2).

4. Major surgical surgery (except biopsy) or incomplete healing of the surgical incision within 4 weeks prior to the first study drug treatment.

5. Known other malignant tumors within 2 years before enrollment (except for cervical carcinoma insitu, superficial noninvasive bladder tumors, breast ductal carcinoma in situ, prostatic intraepithelial neoplasia without evidence of prostate cancer, or curatively treated Stage I nonmelanoma skin cancer)..

6. Patients who are unstable or have symptomatic or progressive central nervous system (CNS) metastasis. Patients with a history of brain metastasis, who are clinically stable and have demonstrated no progression of CNS disease by magnetic resonance imaging (MRI) or computed tomography (CT) (if MRI is not appropriate) can be enrolled (MRI or CT must be performed at least 4 weeks after the last brain radiotherapy).

7. Previous history of interstitial lung disease, drug-induced interstitial lung disease, symptomatic interstitial lung disease or any evidence of active pneumonia on chest CT scan within 4 weeks prior to the first study drug treatment.

8. Known to interfere with the test requirements of mental illness or drug abuse disease.

9. Participants testing positive for HIV are **NOT excluded** from this study, but HIV positive participants who meet the following criteria is eligible:

    - Have CD4+ T-cell counts ≥350 cells/μL;
    - Have not had an opportunistic infection within the past 12 months. Participants on prophylactic antimicrobials can be included in the study;
    - Should be on an established antiretroviral therapy for at least 4 weeks;
    - Have an HIV viral load less than 400 copies/mL prior to enrollment.

10. Participants have active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Note:

    - Participants will be tested for HCV antibody and HBV surface antigen at Screening. Additional HBV and HCV serological testing will be done at the discretion of the investigator;
    - Participants with HBV who have controlled infection (serum HBV DNA PCRthat is below the limit of detection) are permitted. Participants with controlled infections must undergo periodic monitoring of HBV DNA;
    - Participants who are HCV antibody positive who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) may be enrolled into the study. Participants with controlled infections must undergo periodic monitoring of HCV RNA per treating physician.

11. History of clinically significant cardiovascular disease, such as:

- Symptomatic congestive heart failure according to New York Heart Association Grades (NYHA > Grade 2);
- Severe/unstable angina, new angina within last 3 months;
- Myocardial ischemia and long-term use of drugs for control; according to NYHA, grade III-IV cardiac insufficiency;
- Any event of acute myocardial infarction within 6 months before screening;
- Any grade ≥ 2 supraventricular arrhythmia or ventricular arrhythmia requiring treatment or intervention;
- Any grade atrial fibrillation, coronary/peripheral artery bypass graft, or cerebrovascular symptoms including transient ischemic attack;
- QTcF (Fridericia's correction formula used) > 470 ms;
- ECG < 50 bpm.

12. History of serious allergic reactions to the study drugs or excipients used in the protocol.
13. Women who are pregnant or lactating.
14. Prior use of an oral selective estrogen receptor degrader (SERD).
15. Subjects who use drugs or herbal supplements known to be moderate/strong inhibitors of CYP3A 2 weeks or 5 drug half-lives (whichever is longer) prior to the first study drug treatment. Subjects who use drugs or herbal supplements known to be moderate/strong inducers of CYP3A 4 weeks or 5 drug half-lives (whichever is longer) prior to the first study drug treatment.
16. Received medications which inhibits the production of gastric acid within 2 weeks or 5 drug half-lives (whichever is longer) prior to the first dose of study drugs.
17. Other conditions that the investigator considers inappropriately for this study.

Subject Responsibilities

Your participation in this study is voluntary. If you are eligible and enrolled to the study, you will need to:

1. Use effective contraception if sexually active and of child bearing potential. You must commit to using 2 forms of effective contraception at the same time, at least 1 of which must be a highly effective form, from 1 month prior to the first dose until 6 months following the last dose of study drug. Female subjects must also refrain from egg donation and *in vitro* fertilization during the study and until at least 6 months after the last of study drug.

   Discuss this with the Study Doctor, who will give your instructions and suggestions about effective contraception methods.

2. Tell the study staff about any side effects or problems, ask questions as you think of them.

3. If you change your mind about staying in the study, please tell the study team.

4. Not use any drugs of abuse, alcohol, and any tobacco products for the duration of the study.

5. Not use caffeine or xanthine containing food or beverages (coffee, tea, chocolate, energy drinks and colas) 24 hours before dosing and until collection of the final PK samples during each session.

6. Avoid eating grapefruit or grapefruit-containing juice from 5 days before the first dose of study drug until the time of study drug (or EOT).

7. Refrain from strenuous exercise at least 24 hours prior to each blood collection, and be will to avoid extreme exposure of sun and sunbathing (≥ 15 min) during the study.

8. Be willing to have your photo taken for study identification, and photographs taken of possible side effects for study records, if you have visible reactions (e.g. skin rash) to the study drug.

You are responsible for any transportation and/or living costs incurred while traveling to and from the research unit. You cannot participate in any other clinical study during your participation in this study. This is a precaution to protect your safety and the carry out evaluations of this study.

Study Design

This study is divided into 3 parts: Part 1 also called Part A study, is to determine the best dose of monotherapy ("dose escalation as monotherapy phase"), Part 2, also called Part B study to determine the best dose of combination therapy ("dose escalation as combination with palbociclib phase") and Part 3, also called Part C study to use the best dose in more subjects ("dose expansion as monotherapy phase").

- **Part A study**

For Part 1 cohorts A1 through A5, subjects take a single dose of FWD1802 Tablet by mouth with water on Cycle 0 Day 1 (C0D1). For the next 4 days, you will not take a FWD1802 Tablet. These 4 days (Day 2, 3, 4 and 5) are to determine how the body responds to the tablet. After this observation period, the next cycle starts, C1D1. Starting on C1D1, take the assigned dose of the FWD1802 Tablet as instructed by the study staff by mouth with water. Every treatment cycle consists of 33 days.

Starting with Cycle 2 (C2) you will take a dose as instructed every day until instructed to stop taking the tablets up until discontinuation criteria (such as disease progression, death, unacceptable toxicity, withdrawal of informed consent, or other reasons to discontinue study treatment occurs), whichever comes first.

While participating in the study, each subject will have a schedule to report to the study site to see how you are feeling, obtain samples and provide your input about how they are feeling.

- **Part B study**

For all cohorts B1 ~ B2 in Part B, eligible subjects will receive a once-daily dose of FWD1802 combination with palbociclib by mouth with water for 28-days until the subject discontinues the study drug for disease progression, death, unacceptable toxicity, withdrawal of informed consent, or other reasons to discontinue study treatment occurs, whichever comes first. The dose will be determined from the information collected in Part A.

- **Part C study**

For all cohorts C1 ~ C2 in Part C, eligible subjects will receive a once-daily dose of FWD1802 by mouth with water for 28-days until the subject discontinues the study drug for disease progression, death, unacceptable toxicity, withdrawal of informed consent, or other reasons to discontinue study treatment occurs, whichever comes first. The dose will be determined from the information collected in Part A.

If you are assigned to Part A, Cohorts A1, A2, A3, A4, or A5, you will receive one of the following doses given orally in fed state during dose period;

Cohort	Dose	Status	D1, single dose	D7 and thereafter, a consecutive 28 days of each cycle
A1	25 mg	fed	1 × 25 mg/tablet	1 × 25 mg/tablet, QD
A2	75 mg	fed	3 × 25 mg/tablet	3 × 25 mg/tablet, QD
A3	150 mg	fed	1 × 150 mg/tablet	1 × 150 mg/tablet, QD
A4	300 mg	fed	2 × 150 mg/tablet	2 × 150 mg/tablet, QD
A5	450 mg	fed	3 × 150 mg/tablet	3 × 150 mg/tablet, QD

If you are assigned to Part B, Cohorts B1, B2, you will receive one of the following doses determined in Part A orally in fed state from Day 1 to Day 28 per cycle. While the palbociclib dose is the fixed approved dose: 125 mg intake daily, for consecutive 21 days then off for 7 days, which composes 28-day every treatment cycle, which is consistent with the 28-day treatment cycle of the study:

Cohort	Status	Dose taken once/day
B1	fed	TBD+ palbociclib (125mg)
B2	fed	TBD+ palbociclib (125mg)

If you are assigned to Part C, Cohorts C1, C2, you will receive one of the following doses determined in Part A orally in fed state from Day 1 to Day 28 per cycle:

Cohort	Status	Dose taken once/day
C1	fed	TBD

C2	fed	TBD

This is a "open-label" study, which means that you, the investigator and study team will know the information of the study drug (FWD1802) you are given.

The Study Doctor, Study Monitor, and sponsor (Shenzhen Forward Pharmaceuticals Co. Ltd) will review all information and any specific safety issues during the study. They will decide if the current dose level is safe to escalate to a higher one, and if the study is safe to continue from Part A to Part B and Part C. In addition to these reviews, there is an Institutional Review Board (IRB) assigned to this study. IRB members are not part of the study, they provide an ethical review to assess safety and risks to participants.

If changes are made to any of the above cohorts, or cohort(s) are added once you are enrolled, you would be informed of these changes and asked to review and sign a new consent form.

Duration

The timing and total duration depends on the Part and Cohort you are assigned, including up to 28-day screening period prior to the first dose.

Reiterated treatment cycles of 4 weeks until progression disease based on radiological evaluation, undue drug toxicity, withdrawal of consent or death, whichever occurs first.

Procedures and Protocol

Day -28~-1: Screening (for all Parts and all Cohorts)

Before the study starts, you will be asked to sign this consent form, go through the following screening procedures to check for your eligibility for the study. You must answer all questions asked by the staff honestly and completely. If your health condition changes during the screening period, you must inform the study doctor.

To complete the screening assessments, you may need to visit the study site more than one time during this period. Some of assessments include:

- We will ask you how you are feeling and about any medications you have taken;
- We will ask you about your medical history, including any psychiatric, surgical, blood donation, smoking, alcohol and/or drug history;
- The study doctor will review the study requirements to determine your eligibility to participate in this study;
- We will ask you some personal information such as your race, date of birth, etc.;
- Your vital signs (Blood Pressure, Heart Rate, Temperature, and Respiratory Rate) will be measured;
- A physical examination with general appearance, and the following organs and systems: head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest;

respiratory, cardiovascular; lymph nodes; abdomen; skin, hair, nails, musculoskeletal; neurological and mental status, and mental status will be recorded;

- You will be asked how well you are able to perform normal daily living activities. This is called a performance evaluation or a performance status assessment;
- You will have a 12-lead ECG (electrocardiogram – heart rhythm tracing);

Note: Male subjects may need to have their chest hair shaved before the ECGs so the ECG patches will stick to your skin. Female subjects may not be allowed to wear a bra while the ECG tracing is being taken.

- Your weight and height will be measured, and your BMI will be calculated;
- Urine screening test for drugs of abuse, alcohol and tobacco use;
- We will ask you about current use of contraceptives;
- If female, we will ask you about your menstrual cycle; if a female of post-menopausal status, we may collect a blood sample during the screening visit to confirm your post-menopausal status; if you are a female who is able to get pregnant, a blood pregnancy test will be performed;
- You will have blood drawn for lab tests (must not eat or drink anything for at least 12 hours, water only). These tests will be on the blood, include Chemistry tests (such blood sugar, potassium, etc.), Hematology (such as red/white blood cell counts), Coagulation (how quickly your blood clots) and Urinalysis (testing your urine for protein, bacteria, etc.);
- We will assess your tumor and need your archived or new samples of tumor tissues;
- You will be informed of which cohort you will be assigned to, either Part A, Part B or Part C;
- You will be tested for hepatitis B and C, and HIV. If the infectious disease screening is positive, you will be told in private;
- You will using ^{18}F-FES PET to monitor the detect in ER target occupation and inhibition;
- You will be monitoring adverse events and concomitant medication;
- Admission to the phase I CRU.

Completing these procedures does not guarantee your entry into the study. Study entry will depend upon the results of your laboratory tests, study-specific guidelines, and the decision made at the discretion of the study doctor.

If You Are Assigned to Part A

Single Dose (C0D1 to C0D5 for Part A: Cohorts A1~A5)

- Review any changes to your health and/or medications you have taken since being admitted;
- On the Day 1, study drug will be given with approximately 240 mL water, after meal within 30 minutes. The study doctor or staff will inspect the process;
- Weight, body height (only C0D1);
- Physical examination (only C0D1, C0D2, C0D3, C0D4);
- Vital signs (only C0D1, C0D2, C0D3, C0D4);
- ECOG Score (only C0D1, C0D2, C0D3, C0D4);
- 12-lead ECG (only C0D1, C0D2);
- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis (only C0D1). The tests of hematology, urinalysis, blood biochemistry and coagulation before the first dose administration could be exempted if the tests planned during the screening period were performed within 3 days before the first administration on C0D1. Other examinations may be conducted if deemed clinically necessary by the investigator;
- Collect PK blood samples at multiple time points (only C0D1, C0D2, C0D3, C0D4, C0D5).

Multiple doses (Cycl 1, Cycle 2, ⩾Cycle3) for Part A: Cohorts A1~A5)

- Review any changes to your health and/or medications (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);
- Starting on Cycle 1 Day 1 (C1D1), FWD1802 Tablet will be orally administered continuously for 28 consecutive days in each cycle, study drug will be given with approximately 240 mL water, after meal within 30 minutes. The study doctor or staff will inspect the process.
- Weight, body height (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);
- Physical examination (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);
- Vital signs (only C1D1, C1D2, C1D8, C1D15, C2D1, (C3~Cn) D1);
- ECOG Score (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);
- 12-lead ECG(only C1D15, C1D16, C2D1, (C3~Cn) D1);
- Echocardiogram (only C1D1, CnD1(every 8 weeks));

- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis) (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);
- Collect PK blood samples at multiple time points (only C1D1, C1D8, C1D15, C1D16, C2D1, C3D1);
- We will assess your tumor (During the treatment period, imageological examination and efficacy assessment should be repeated every 8 weeks (± 7 days) from C1D1 for the first 12 months, then every 12 weeks (± 7 days) thereafter until disease progression);
- ^{18}F-FES PET/CT (only C2D1);
- You can leave the study site if all assessments are completed with the Study Doctor permission.

Follow-Up: EOT visit (for Part A: Cohorts A1~A5)

- Review any changes to your health and/or medications;
- Weight, body height;
- Physical examination;
- Vital signs;
- ECOG Score;
- 12-lead ECG;
- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis);
- You can leave the study site if all assessments are completed, with the Study Doctor permission.

Follow-Up: SFU visit, LTFU visit (for Part A: Cohorts A1~A5)

- Review any changes to your health and/or medications;
- We will ask about your subsequent anti-tumor therapy;

If You Are Assigned to Part B

Multiple dose (Cycl 1, Cycle 2, ≥Cycle3) for Part B: Cohorts B1~B2)

- Review any changes to your health and/or medications you have taken since being admitted;
- Study drug and Palbociclib tablet (Palbociclib dose is the fixed approved dose: 125 mg intake daily, for consecutive 21 days then off for 7 days, which composes 28-day treatment cycle, which is consistent with the 28-day treatment cycle of

FWD1802. Every treatment cycle consists of 28 days) will be given with approximately 240 mL water after meal;

- Weight, body height (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);;
- Physical examination (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);;
- Vital signs (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);;
- ECOG Score (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);;
- 12-lead ECG (only C1D1, C1D2, C1D15, C1D16, C2D1, (C3~Cn) D1);;
- Echocardiogram (every 8 weeks);
- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis) (only C1D1, C1D8, C1D15, C2D1, (C3~Cn) D1);
- Collect PK blood samples at multiple time points (only C1D1, C1D2, C1D8, C1D15, C1D16, C2D1, C3D1); ;
- We will assess your tumor (During the treatment period, imageological examination and efficacy assessment should be repeated every 8 weeks (± 7 days) from C1D1 for the first 12 months, then every 12 weeks (± 7 days) thereafter until disease progression);
- ^{18}F-FES PET/CT (only C2D1);
- You can leave the study site if all assessments are completed with the Study Doctor permission.

Follow-Up: EOT visit (for Part B: Cohorts B1~B2)

- Review any changes to your health and/or medications;
- Weight, body height;
- Physical examination;
- Vital signs;
- ECOG Score;
- 12-lead ECG;
- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis);
- Return the diary card and reminder of post-study instructions, including birth control, pregnancy reporting, etc.
- You can leave the study site if all assessments are completed, with the Study Doctor permission.

Follow-Up: SFU visit, LTFU visit (for Part A: Cohorts A1~A5)

- Review any changes to your health and/or medications;
- We will ask about your subsequent anti-tumor therapy;

If You Are Assigned to Part C

Multiple dose (Cycl 1, Cycle 2, ≥Cycle3) for Part C: Cohorts C1~C2)

- Review any changes to your health and/or medications you have taken since being admitted;
- Study drug will be continuous dosing with approximately 240 mL water after meal;
- Weight, body height (C1D1, C2D1, (C3~Cn) D1);
- Physical examination (C1D1, C2D1, (C3~Cn) D1);
- Vital signs (C1D1, C2D1, (C3~Cn) D1);
- ECOG Score (C1D1, C2D1, (C3~Cn) D1);
- 12-lead ECG (C1D1, C2D1, (C3~Cn) D1);
- Echocardiogram (every 8 weeks);
- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis) (C1D1, C2D1, (C3~Cn) D1);
- Collect PK blood samples at multiple time points (C1D1, C2D1, C3D1);
- We will assess your tumor (During the treatment period, imageological examination and efficacy assessment should be repeated every 8 weeks (± 7 days) from C1D1 for the first 12 months, then every 12 weeks (± 7 days) thereafter until disease progression);
- ^{18}F-FES PET/CT (only C2D1);
- You can leave the study site if all assessments are completed with the Study Doctor permission.

Follow-Up: EOT visit (for Part C: Cohorts C1~C2)

- Review any changes to your health and/or medications;
- Weight, body height;
- Physical examination;
- Vital signs;
- ECOG Score;

- 12-lead ECG;
- Laboratory assessments (including blood chemistry, hematology, coagulation, urinalysis);
- You can leave the study site if all assessments are completed, with the Study Doctor permission.

Follow-Up: SFU visit, LTFU visit (for Part A: Cohorts A1~A5)

- Review any changes to your health and/or medications;
- We will ask about your subsequent anti-tumor therapy;

HIV and Hepatitis Testing

You must have your blood tested for Hepatitis B and C viruses and for HIV in order to participate in the study. This is done to protect the safety for the study team who will be collecting and handling your blood and other samples. Human Immunodeficiency Virus (HIV) is the virus that can cause Acquired Immunodeficiency Syndrome (AIDS). A blood test can show if you have been exposed to, or are infected with HIV by checking for the virus (antigen) or antibodies. Antibodies are substances produced by the body's immune system to fight infection.

Agreeing to have the HIV and hepatitis virus tests done is a voluntary decision that only you can make. However, if you choose not to have those tests performed, you will not be able to participate in this study. The HIV and Hepatitis B and C virus tests will be done confidentially. A positive HIV result does not mean that you have HIV or AIDS, and a negative test result does not mean that you are not infected because it can take up to three months for some tests to indicate infection. Positive results for HIV or Hepatitis B/C virus must be reported to a local health agency. This is the legal obligation of health professionals in this state.

If you are disqualified for study participation by other screening procedures or if you do not complete the screening visit, it is possible that those tests will not be completed.

Possible Side Effects and Risks

If you do not understand what any of these side effects mean, please ask the Study Doctor or any study staff to explain these terms to you.

Because the study drug, FWD1802, is investigational, all the side effects may not be known. There may be rare and unknown side effects. Some of these may be life-threatening. However, we will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicine to decrease the symptoms of the side effects or reactions. Or we may stop the use of one or more drugs. If this is necessary, we will discuss it together with you and you will always be consulted before we move to the next step.

You must tell the Study Doctor or study staff about all side effects that you have. If you are not honest about your side effects, you may harm yourself by staying in this study.

You may be asked to return to the clinical unscheduled safety follow-up visits or biological samples if deemed necessary by the study doctors.

What are the Possible Side Effects or Harms of Taking Part?

The following information describes side effects observed in animals. It is unknown whether these side/adverse effects observed in animal studies will also be observed in human study participants.

Risks Seen in Animal Studies

The fertility effects of study drug have not been fully studied. So, if you are a male and agree to participate in this study, you will be asked to avoid fathering a child or donating sperm until at least 90 days after your last dose of study drug. If you are a female and agree to participate in this study, you will be asked to avoid becoming pregnant from at least 1 month prior to the study until 6 months after your last dose of study drug.

Results from animal studies indicate there is a potential risk of body weight change, bilateral conjunctiva hyperemia and/or ocular discharge. There were also observations of changes in hematology (increased eosinophils,basophils and neutrophils). All side effects almost disappeared or showed improvement after study drug was stopped.

Risks of Other Drugs like FASLODEX® (Fulvestrant)

The most common adverse reactions occurring in ≥5% of patients receiving FASLODEX 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of FASLODEX patients and were not dose-dependent.

Risks of Other Drugs like ORSERDU (elacestrant)

The most common (>10%) adverse reactions, including laboratory abnormalities, of ORSERDU were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

Additional Risk or Discomforts

Blood sample collection:

Blood samples will be taken by single needle-sticks or indwelling needle in the upper arm.

Blood samples will be taken approximately 29 times (Part A Cohorts A1-5), approximately 25 times (Part B Cohort B1~B2), or approximately 6 times (Part C Cohorts C1-2) throughout the course of the study. If 3.5 mL/time, a total of approximately 101.5 mL (Part A cohorts A1-5), approximately 87.5 mL (Part B Cohort B1~2), or approximately 21 mL (Part C Cohort C1~2) of blood will be drawn throughout the study. For women of childbearing potential require additional serum

pregnancy test (1 time, 3.5 mL). Additional blood samples may be required if any of your laboratory tests are abnormal. It is possible that more than one attempt to obtain a blood sample may be necessary.

For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 500 mL (about two cups) of blood. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health.

There may be side effects or discomforts of having blood drawn, such as: fainting, redness, pain, bruising, bleeding, infection, nerve damage, and blood clots, which may cause inflammation, swelling and pain.

If you feel faint tell the study staff right away.

What if New Information Becomes Available?

If any new information about study drug, study procedures or risks becomes available which could affect your willingness to participate or which have an impact on your follow-up, the study doctor will discuss what this will mean for you. If you choose to continue, you may have to sign an updated informed consent. If you choose to discontinue, the study doctor will decide for your future care and treatment.

Birth Control, Dangers of Pregnancy and Breastfeeding

Male or female subjects who plan to have children from signing informed consent until 6 months after last administration should not participate in the study. Females who are pregnant or breastfeeding must not participate in this study.

Even if you use birth control during the study, there is a chance you could become pregnant. If you are pregnant or become pregnant during the study, the study drug may involve unforeseeable risks to the unborn baby. A pregnancy test is not always right, especially in the early stages of pregnancy.

If you are a female, you must not get pregnant while in this study. The only certain way to not get pregnant is to not have sex. You can choose to practice true abstinence, when this is the preferred and usual lifestyle; not just while on the study

If you are a female and choose to have sex, you must use at least 2 forms of birth control listed below. Females must meet one of the following criteria to participate in the study.

- Post-menopausal defined as no menses for ≥ 12 months after stopping all hormone treatments and with follicle stimulating hormone (FSH) level in the post-menopausal range (confirmed by lab test);

- Irreversible surgical sterilization (but not tubal ligation only);

- If of child bearing potential, you and your male partner must agree to use at least 2 forms of effective birth control methods listed below, and one of them must be highly effective form, starting from 1 months prior to the study until at least 6 months after your last dose of study drug.

Highly effective forms of birth control include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral; intravaginal; transdermal. OR
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral; injectable; implantable.
- Note: hormonal contraception may be susceptible to interaction with the IND product, which may reduce the efficacy of the contraception method.
- Intrauterine device.
- Tubal sterilization.
- Essure micro-insert system (provided confirmation of success 3 months after procedure).
- Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure).

Less effective forms of birth control include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

Note: a combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier) are also considered acceptable, but not highly effective, birth control methods.

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. Female condom and male condom should not be used together.

You must also refrain from egg donation and *in vitro* fertilization during the study and until at least 30 days after the last of study drug.

If at any time during the study, you think you may be pregnant, you must immediately contact the study doctor or study staff. We may follow your pregnancy outcome, with your permission.

Possible Benefits

There may not be any benefit for you, but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

Alternatives to Participating in the Study

Since this study is for research only, the only other choice would be not to be in the study.

Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The research center, including the study doctor and staff, must get your permission to use or give out any health information that might identify you (protected health information). By signing this form, you allow the research center to use your information to carry out the study and to share your information for the study, as described in this form.

Photo Release Consent

Photographs may be taken to identify subjects and document side effects, such as a rash, for this study. You give the company paying for this research study the right to use, copy, and give out any pictures taken of you.

Your pictures may be used in scientific journals or magazines.

Your pictures may be used as part of a larger presentation, along with other pictures, videotapes or things like that. Your pictures may also be edited.

The company pay for this research study may give other people or companies permission to use your pictures.

We will try our best to hide your identity. Your name will not be on the pictures. You have the right to review your pictures.

Protecting the Privacy of Your Health Data

The medical information obtained in this study that identifies you will be handled with the strictest confidence. It will be protected as required by laws and/or regulations. It will not be made publicly available. Certain people and organizations will need to see, copy and use your health data so that they can do their part in the study, and some of these people and organizations will see your health data together with information that identifies you. This is necessary to ensure the trial is conducted properly, to verify the accuracy of data collected from you and for regulatory purposes. They are called “authorized users”. Authorized users will be given access to and may make copies of your health data. In general, before the information about your health leaves the research clinic facility, it will be labeled with a code identifying you only by study subject number, and will not contain full name, or other items that could identify you personally; however, there may be circumstances that require your health information along with information that identifies you be disclosed to authorized users outside of the study locations. Specimens of your blood or other samples will also be labeled with your subject number and will not be labeled with your name. The following people will have access to your study records and will use the information for purposes of conducting the study, for regulatory purposes or as described below.

The following people will have access to your study records:

- The study doctor and the study staff;
- Sponsor company, the sponsor's associated companies, and representatives;
- The United States Food and Drug Administration (FDA);
- Other country, state or federal regulatory agencies;
- Institutional Review Board (IRB).

A description of this clinical trial will be available on https://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this web site at any time.

The IRB and accrediting agencies may inspect and copy your records, which may have your name on them. Therefore, total confidentiality cannot be guaranteed. If the study results are presented at meetings or printed in publications, your name will not be used.

Disclosure is permitted only when:

- Required by Federal, State, or local laws (e.g., as required by the FDA or state laws requiring the reporting of communicable diseases to State and local health departments);
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains;

OR

- Made for the purposes of other scientific research that follows regulations governing the protection of human subjects in research.

You or a member of your family will not be prevented from voluntarily releasing information about yourself or your involvement in this study. If you give your consent to release information to a medical care provider, an insurer, or other person to receive study information, then the study staff will not withhold that information.

In Case of Study Related Injury

If you are injured during your participation in this study, you should contact the study doctor as soon as possible. Contact the study doctor in person or at the telephone number listed on page one of this consent form. If you need immediate medical care, you should seek it in the same way you would ordinarily get emergency medical treatment.

If you suffer a study-related injury, the reasonable costs of necessary medical treatment of the injury may be reimbursed to the extent these costs are covered by your private insurance or other third party coverage. A study-related injury is a physical injury that is directly caused by the study drug that has been given as described in the study protocol or by medical procedures that are required by the study. The study team do not provide long-term medical care or financial compensation for study-related injuries.

Injuries directly caused by any of the following are not considered study-related injuries:

- The natural course of a disease or medical condition that you already had or have;
- Not following the instructions provided in this consent form or by study staff.

No other forms of payment or compensation are offered for study-related injuries (for example, for lost wages or discomfort).

No other form of compensation is offered for non-study related injuries.

Costs for Being in the Study

There is no cost to you for participating in the study.

Payment for Being in the Study

You will not be paid for taking part in this study and will not be compensated for any lost time from work.

Legal Rights

You will not lose any of your legal rights by signing this consent form.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. You may change your mind later and stop participating even if you agreed earlier. You may want to inform your personal doctor of your choice to participate in this study.

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

The Study Doctor, the sponsor, IRB, or the FDA may take you out of the study without your permission, at any time, for the following reasons:

- If you do not follow the study staff's instructions;
- If we find out you should not be in the study;
- If the study is stopped;
- If it becomes harmful to your health.

If you leave the study or if you are taken out of the study, you may be asked to have some end of study evaluations, tests or biospecimen.

Who to Contact

If you have questions, concerns, or complaints about this study or to report a study related injury, contact:

DAYTIME/AFTER HOURS:

If you are unable to reach anyone at the number(s) listed above and you require immediate (life threatening) medical attention, please go to the nearest emergency room.

This proposal has been reviewed and approved by Salus (IRB), which is a committee whose task is to make sure that research participants are protected from harm. If you do not want to talk to the Study Doctor or study staff, if you have concerns or complaints about the research, or to ask questions about your rights as a study subject you may contact IRB. IRB's policy indicates that all concerns/complaints are to be submitted in writing for review at a convened IRB meeting to:

Mailing Address: XX

Email Address: xx

If you are unable to provide your concerns/complaints in writing or if this is an emergency regarding subject safety, contact the office at: xx.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART II:

Agreement To Be In The Study

Statement by the Study Subject

This consent form contains important information to help you decide if you want to be in the study. If you have any questions that are not answered in this consent form, ask one of the study staff.

Please answer YES or NO to the following statements:

A. I have read the above information in a language that I understand well. _____

B. The content and meaning of this information have been explained to me. _____

C. I have been given an opportunity to ask my questions in private as well as to meet with a study doctor to discuss this study. _____

D. I have asked the staff any questions I may have and any questions that I have asked have been answered to my satisfaction. _____

E. **I have had enough time to decide if I want to take part in this study.** _____

F. I understand I do need to agree the photo release in order to be in the study _____

G. **I also agree to the HIV testing as described in this document.** _____

H. I understand that I can leave the study at any time without giving a reason and without affecting my health care. _____

I. I hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of my medical information. _____

IF YOU ANSWERED '**NO**' TO ANY OF THE ABOVE STATEMENTS, OR YOU ARE UNABLE TO ANSWER ANY OF THE ABOVE STATEMENTS, YOU SHOULD NOT SIGN THIS CONSENT FORM.

_____

Printed Name of Adult Study Subject

_____

Signature of Adult Study Subject Time Date

Statement by the Researcher/Person Explaining Consent Form

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the procedures that this study will do.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Printed Name of Person Explaining Consent Form

Signature of Person Explaining Consent Form Time Date

I have received a signed and dated copy of this study consent form to keep.

Your Signature Date

To be Completed by Covance Staff Only:

QC'd by _____

Date _____