Clinical Study Protocol

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:	FWD1802-001C
Version/Date:	1.1/July 13, 2023
Investigational Product:	FWD1802
Study Phase:	Phase I
Sponsor:	Shenzhen Forward Pharmaceuticals Co. Ltd B406, 19 Gaoxin S. 7th Ave., ShenZhen Hi-Tech Industrial Park, ShenZhen, Guangdong Province, P.R. China
Contact:	Chenggang Zhu 8618621958197 zhucg@forward-pharm.com

informed consent from those persons to whom the drug may be administered, a general protocol description may be disclosed to such potential subjects.

Sponsor Statement

Study Protocol 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 Number: 1.1

Investigational Product: FWD1802

Sponsor: Shenzhen Forward Pharmaceuticals Co. Lt

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

The following signature documents this approval.

Jin Liu

_____ _____

Representative of Sponsor Date

Title CSO

Shenzhen Forward Pharmaceuticals Co. Lt

Investigator Agreement

Study Protocol Title:

Protocol Number:

Version Number:

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor.

I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

The ethical principles that have their origin in the Declaration of Helsinki.

International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.

All applicable laws and regulations, including, without limitation, data privacy laws and regulations.

Principle Investigator:

Name (Print):

Clinical Study Center:

Signature _____ Date _____

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Synopsis

Investigational Product	FWD1802
Protocol Number	FWD1802-001C
Version/Date	1.1 / Jul 13 2023
Sponsor	Shenzhen Forward Pharmaceuticals Co. Lt
Number of Subjects	Approximately 99 patients
Study Population	A/B: ER+ /HER2- unresectable locally advanced or metastatic breast cancer. C: ER+/HER2- unresectable locally advanced or metastatic breast cancer with ESR1 mutation
Study Objectives	**Primary Objective:** • Establish the recommended phase II dose (RP2D) and/or the maximum tolerated dose (MTD) of FWD1802 as monotherapy and in combination with palbociclib in patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer. • Explore the safety and tolerability of FWD1802 as monotherapy and in combination with Palbociclib. **Secondary Objective:** • Characterise Pharmacokinetics of FWD1802 as monotherapy and in combination with palbociclib. • Explore the metabolic pathway of FWD1802. • Explore preliminary efficacy signals. **Exploratory Objective:** • Biomarker of FWD1802 as monotherapy and in combination with palbociclib.
Starting Dose Selection	According to ICH S9, considering the safety, efficacy of the nonclinical studies, and drug formulation specifications, in a more conservative way, 25 mg was proposed as the starting dose. The details of starting dose in this protocol please refer to Section 1.3.1 Rational for Dose Regimen of Escalation

Study Design	Open-label dose escalation trial of monotherapy and combination therapy with expansion. The overall study design is presented graphically in Figure 1. Detailed research procedures can be found in Section 7 Research Procedures. Part A is an open-label, dose escalation of FWD 1802 as monotherapy, approxiamately 27 patients. Dose escalation steps will be determined by the Safety Monitoring Committee (SMC), based on 3+3 rule except for the accelerated escalation on the 1st dose level. With pharmacokinetic (PK), pharmacodynamics (PD), efficacy and safety data, SMC will evaluate to guide determination of potentially effective dose for part B and C. Part B is an open-label, dose escalation of FWD 1802 in combination with palbociclib fixed dose, approxiamately 12 patients in no more than 2 dose levels. Dose escalation steps will be determined by SMC, based on 3+3 rule. With PK, PD, efficacy and safety data, SMC will evaluate to guide determination of potentially effective combination dose. Part C is an open label, dose expansion of FWD 1802 monotherapy on patients with ER+/HER2-/ESR1 mutation, no more than 2 dose levels will be evaluated, with 30 patients at the most in either dose level cohort.
Investigational Product and Administration	FWD1802 • Dosage Formulation: Tablet • Specification: 5 mg, 25 mg, 150 mg • Dosage Regimen: oral, once daily (QD). For details of dosage regimen for 8.2 Meals and Dietary Restrictions. • Storage: sealed containers, dry, ≤25℃, keep out of light.
Inclusion Criteria	1. Patients must understand and voluntarily sign the Informed Consent Form (ICF). 2. Patients ≥ 18 years, 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 is eligible (See Appendix 6). 4. Documented positive oestrogen receptor status of primary or metastatic tumour tissue, according to the local laboratory

	parameters. HER-2 negative. 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) and progesterone receptor (PgR) testing in breast cancer (Allison et al., 2020). 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: Previous therapy failed or intolerable, or standard therapy not available. Part B/C: 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(See Appendix 6). 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): a) Blood routine: Absolute neutrophil count (ANC) ⩾ 1.5×10^9/L; Platelet count (PLT) ⩾100×10^9/L; Hemoglobin (HGB) ⩾ 90 g/L; b) Liver 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 or AST⩽ 5×ULN with liver metastasis; c) Renal function: Serum creatinine ⩽ 1.5×ULN or estimated creatinine clearance (CLcr) ⩾ 60 mL/min as calculated using Cockcroft-Gault formula; d) Coagulation function: Activated Partial thromboplastin Time (APTT) and international normalized ratio (INR) ⩽ 1.5×ULN (or within target range if on anticoagulation therapy); e) 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).
Exclusion Criteria	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, Or receive mitomycin and nitrosourea within 6 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 $\leqslant$ 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. Subjects with unstable or symptomatic or progressive Central nervous system (CNS) metastasis. Subjects with a history of brain metastases who were clinically stable and who underwent Magnetic resonance imaging (MRI) or Computed tomography (CT) Subjects with CT (if not suitable for MRI) who confirm no CNS disease progression 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. History of human immunodeficiency virus HIV infection, or active bacterial or fungal infection requiring systemic treatment within 14 days prior to the first study drug treatment.

	10. Presence of active syphilis infection. 11. Subjects with known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection with abnormal liver function (Absence of infection was defined as HBsAg negative, HBV DNA negative and HCV antibody negative), except to: • Subjects who test positive for HBsAg or HBsAb during the screening period may be enrolled if the PCR test result for HCV-RNA is < 500 IU/ml (2000 copies/mL), but receive antiviral treatment according to the investigator's assessment and undergo PCR for HBV-DNA during the study treatment period; • Subject has a positive test for HCV antibody at screening and can be enrolled if the PCR test result for HCV-RNA is negative. 12. History of clinically significant cardiovascular disease, such as: a) Symptomatic congestive heart failure according to New York Heart Association Grades (NYHA > Grade 2); b) Severe/unstable angina, new angina within last 3 months; c) Myocardial ischemia and long-term use of drugs for control; according to NYHA, grade Ⅲ-Ⅳ cardiac insufficiency; d) Any event of acute myocardial infarction within 6 months before screening; e) Any grade ≥ 2 supraventricular arrhythmia or ventricular arrhythmia requiring treatment or intervention; f) Any grade atrial fibrillation, coronary/peripheral artery bypass graft, or cerebrovascular symptoms including transient ischemic attack; g) QTcF (Fridericia's correction formula used) > 470 ms; h) ECG < 50 bpm. 13. History of serious allergic reactions to the study drugs or excipients used in the protocol. 14. Women who are pregnant or lactating. 15. Prior use of an oral selective estrogen receptor degrader (SERD).

<table>
<tr><td></td><td>16. Subjects who use drugs or herbal supplements known to be moderate/strong inhibitors of CYP3A2 weeks prior to the first study drug treatment. Subjects who use drugs or herbal supplements known to be moderate/strong inducers of CYP3A4 weeks prior to the first study drug treatment.

17. Received medications which inhibits the production of stomoch acid within 2 weeks or 5 drug half-lives (whichever is longer) prior to the first dose of study drugs.

18. Received medications which inhibits P-gp within 2 weeks or 5 drug half-lives (whichever is longer) prior to the first dose of study drugs.

19. Patients with active or chronic corneal disease, other active eye disease requiring ongoing treatment, or any clinically significant corneal disease for which drug-induced keratopathy cannot be adequately monitored.

20. Other conditions that the investigator considers inappropriately for this study.</td></tr>
<tr><td>Study Procedure</td><td>This study consists of three phases: dose escalation as monotherapy phase, combination with palbociclib phase and dose expansion as monotherapy phase. Details please refer to 7 Study Procedures.</td></tr>
<tr><td>Dose/regimen</td><td>• Part A:

Dose tiers will start at 25 mg, with daily oral administration.

Every treatment cycle consists of 28 days.

Dose-escalation steps will be determined by SMC. The dose level, dose frequency, regimen could be modified based on the PK, safety and preliminary efficacy.

The scheduled dose level and patient number as below：

<table>
<tr><td>Dose cohort</td><td>Daily dose (mg)</td><td>Patient number</td></tr>
<tr><td>1</td><td>25</td><td>1-3 (accelerated escalation)</td></tr>
<tr><td>2</td><td>75</td><td>3-6</td></tr>
<tr><td>3</td><td>150</td><td>3-6</td></tr>
<tr><td>4</td><td>300</td><td>3-6</td></tr>
<tr><td>5</td><td>450</td><td>3-6</td></tr>
</table>
• Part B:

The starting dose of FWD1802 will be the recommended monotherapy dose which is deemed safety and decided by SMC based on the</td></tr>
</table>

	comprehensive evaluation from part A based on PK, PD and preliminary efficacy. The dose level of FWD1802 to be combined with palbociclib is to be determined by SMC. 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 treatment cycle, which is consistent with the 28-day treatment cycle of FWD1802. Every treatment cycle consists of 28 days. The dose level, dose frequency, regimen could be modified based on the PK, safety and preliminary efficacy. No more than 2 dose level cohorts of FWD 1802 will be selected for the combination with palbociclib. The dose adjustment is referred to the SmPC. • **Part C:** No more than 2 dose levels determined from Part A and deemed safety by SMC will be explored further in part C in parallel with Part A, the planned patient number in every dose level cohort is 30 at the most , which will be determined by SMC.Every treatment cycle consists of 28 days.
Mode of administration	Oral (P.O)
Test product(s)	FWD1802
Combination product(s)	Palbociclib
DLT Definition / MTD evaluation period	**DLT Definition:** All AEs of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes. **1. Hematological toxicity:** • CTCAE Grade ≥4 thrombocytopenia; • CTCAE Grade 4 neutropenia lasting >7 days; • CTCAE Grade ⩾3 febrile neutropenia, where Grade 3 febrile neutropenia is defined as ANC <1000 / mm^3 and a single temperature

	of >38.3° C (101° F) or a sustained temperature of ≥38° C (100° F) for more than one hour; • CTCAE Grade 3 thrombocytopenia (≥ 25,000/mm^3 and <50,000/mm^3) associated with bleeding; **2. Non-hematological toxicity:** • Hy's law, defined as: ✧ AST or ALT > 3 x the upper limit of normal (ULN) AND ✧ Total bilirubin > 2 x ULN AND ✧ Alkaline phosphatase < 2 x ULN AND ✧ No other reason for liver injury • ALT or AST >8x ULN, ALT or AST >5x ULN for more than 2 weeks, ALT or AST >3x ULN and (TBL >2x ULN or INR >1.5) ✧ For patients with hepatic metastases, AST or ALT > 8 x ULN or AST or ALT > 5 x ULN for ≥ 14 days • Grade > 3 non-hematologic toxicity with the exception of the following ✧ Grade 3+ fatigue ≥7 days regardless of baseline grade； ✧ Grade 3 nausea and vomiting, lasting ≤ 2 days with optimal medical management； ✧ Grade 3 diarrhea lasting ≤ 3 days with optimal medical management ✧ ≥ 3+ non-hematologic abnormalities should also include laboratory values that cause symptoms. **MTD Evaluation period：** • Part A: FWD1802 single dose run-in period (C0:D1-D6 intake on D1, then off until D6) and 1st 28-day treatment cycle (C1:D1-D28), total of 34 days; • Part B: the 1st treatment cycle of FWD1802 in combination with palbociclib (C1:D1-D28)

Duration of treatment	Reiterated treatment cycles of 4 weeks until progression disease based on radiological evaluation, undue drug toxicity, withdrawal of consent or death, whichever occurs first.
PK/PD Sample	Please see Section7.5.1 PK Samples and Section 7.3.7 18F-FES PET/CT.
Statistical Methods	Descriptive analysis (summary statistics) will be used to describe the safety and efficacy endpoints. **Safety Analysis:** • Incidence and severity of adverse events according to the NCI-CTCAE (V5.0) will be summarized and displayed in number/percentage. The exposure extent to the study drug will be displayed.. **Efficacy Analysis:** • The ORR and its exact 95% Clopper-Pearson confidence interval will be calculated. The CBR, DCR will also be calculated similarly. All of the time-to-event data (PFS, DOR,OS) will be estimated using Kaplan-Meier method, and the median along with two-sided 95% CI will be displayed(use the Greenwood's formula for estimation of standard errors). **Pharmacokinetic analysis:** • A descriptive analysis of the plasma concentration and derived PK parameters of FWD1802 and its metabolite (if possible) will be conducted by dose level. Plasma concentration patient profiles versus time and mean concentration versus time will be displayed.

Table 1 Schedule of Events in Part A Dose Escalation

Items	Screening[1]	Single dose			Multiple dose							Follow-up		
		4 days			Cycle 1 28days				Cycle 2		≥Cycle3	EOT[2]	SFU[3]	LTFU[4]
Visit Day	**D-28~ D-1**	**D 1**	**D2~ D4**		**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D 1**			
Evaluation Window (Days)	0	0	0	0	0	± 1	± 1	± 1	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X X													
Demographics	X													
Medical history	X													
Concurrent diseases	X													
Clinical Procedures/Assessments														
Weight	X	X			X	X	X	X	X	X	X	X		
Body height	X	X			X	X	X	X	X	X	X	X		
Physical examination[5]	X	X	X		X	X	X	X	X	X	X	X		
Vital signs[6]	X	X	X		X	X	X	X	X	X	X	X		
ECOG Score	X	X	X		X	X	X	X	X	X	X	X		
12-lead ECG[7]	X	X			X	X	X	X	X	X	X	X		
Echocardiogram	X				X						X (Every 3weeks)			
Laboratory Assessments														
Blood Chemistry	X	X*			X	X	X	X	X	X	X	X		
Hematology	X	X*			X	X	X	X	X	X	X	X		
Coagulation	X	X*			X	X	X	X	X	X	X	X		
Urinalysis	X	X*			X	X	X	X	X	X	X	X		
Virology: HBV, HCV, and HIV[8]	X													
Pregnancy[9]	X													
COVID-1910	X													

Items	**Screening[1]**	**Single dose**			**Multiple dose**							**Follow-up**		
		4 days			**Cycle 1 28days**				**Cycle 2**		**≥Cycle3**	**EOT[2]**	**SFU[3]**	**LTFU[4]**
Visit Day	**D-28~ D-1**	**D 1**	**D2~ D4**		**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D 1**			
Evaluation Window (Days)	0	0	0	0	0	± 1	± 1	± 1	± 3	± 3	± 3	± 7	± 7	± 7
PK Assessments														
PK Blood Samples[11]		X	X		X	X	X		X		X			
Efficacy Assessments														
Tumor Assessmen[12]	X				X (End of every 8 weeks in the first year; and every 12 weeks thereafter)									
Biomarker Exploration														
18F-FES PET/CT[13]	X								X					
FWD1802 Tablet		X			Continuous Dosing									
Adverse Events	X													
Concomitant Medications and Non-Drug Supportive Interventions	X													

Note: * 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.

1. Screening assessments are performed within 28 days before C0D1. Screening assessments performed no more than 4 days before C0D1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

2. The end-of-treatment (EOT) will occur at the earliest day possible within 7 days after the last dose of FWD1802 or the subject decides to withdraw from study treatment for any reason.

3. Safety follow-up (SFU) visit should be performed at 28 ±7 days after the last administration and prior to the initiation of a new anti-tumor therapy. Subjects who discontinue the study due to an unacceptable adverse event should be followed until AE relieves to grade 0-1 or AE is stable. If EOT visit is within the safety follow-up window, no further safety follow-up is required.

4. LTFU (long term follow-up) visit is for survival follow-up. LTFU visit will performed every 12(±7) weeks after completion of SFU (phone contact is acceptable if the patient cannot return to the site).

5. Physical examination includes examination of whole human body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, abdomen, back, musculoskeletal, orientating neurologic, and psychiatric systems).

6. Vital signs include temperature, pulse, breathing and blood pressure. On C0D1 and C1D1, the vital signs will be measured at pre-morning dose(s), and 0.5 h, 2 h, 4 h, 8 h, 12 h and 24 h after the morning dose(s). On C0D3, C0D4, C1D8, C1D15, C1D22, C2D1, C2D15, (C3~Cn) D1, the vital signs will be measured at pre-morning dose(s). Other examinations may be conducted if deemed clinically necessary by the investigator.

7. 12-lead ECG will be performed three times at Screening, 30 min, 20 min and 10 min pre-dose and 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h and 24 h post-dose on C0D1 and C1D1, and the spacing between each ECG examination will be at least 1 min. On C1D8, C1D15, C1D22, C2D1, C2D15, (C3~Cn) D1, the 12-lead ECG will be measured at pre-morning dose(s) and 2 h after the morning dose(s). Meanwhile, 12-lead ECG will be performed on prematurely withdrawn. If QTcF > 450 ms (male) or > 470 ms (female), 3 consecutive ECGs should be collected to calculate the mean QTcF value.

8. Human immunodeficiency virus antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and Treponema pallidum antibody. period and may optionally be done at additional time points depending on investigator discretion.

9. Only applicable to women of childbearing age; Subjects must have a negative blood pregnancy test during the screening period. Pregnancy tests will be performed anytime during the course of the study, as per investigator’s discretion. Serum or urine tests are acceptable based on the site’s standard clinical practice, if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

10. Infectious disease screening includes polymerase chain reaction for SARS-CoV-2;

11. Blood will be collected for PK analysis of the FWD1802 Tablet and/or its metabolites (if any), details please refer to 7.5.1 PK Samples.

12. Tumor assessment: All patients will undergo MRI, chest, abdomen, pelvis and bone examination at baseline period, and subsequent imageological examination included the chest, abdomen, pelvis, and other metastatic sites, if any. The preferred

imaging methodology is CT enhanced scan, and using the same imaging examination method and examination conditions before and after the same lesion (including scanning slice thickness, contrast agent, etc.). However, If patient has a contrast allergy or intolerance to contrast medium, a plain CT scan is allowed. 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. Each imaging examination should be performed in accordance with the original imaging schedule, without adjustment due to dose delay. Tumor assessments will continue until disease progression and will not be interrupted due to discontinuation of the study treatment.

- CT/MRI examination in the screening period should be confirmed by the sponsor to be acceptable with the test results before the C0D1 meeting the requirements (including the test results before the subject signs the informed consent form).

- Bone scan should be performed during the screening period. The bone scan during the screening period was performed by the sponsor to confirm the results of the research hospital within 42 days before the C0D1 that could meet the research requirements (including the results of the examination before the subject signed the informed consent). Bone scan was performed only when there were clinical indications during the study period.

- The investigator may perform off-schedule imaging assessment at any time when disease progression is suspected. Subjects with a first CR or PR should be confirmed by imaging confirmation or the next efficacy evaluation after at least 4 weeks.

13. Using 18F-FES PET to monitor the detect in ER target occupation and inhibition.

Table 2 Schedule of Events in Part B Dose Escalation

Items	Screening[1]	Escalation							Follow-up		
		Cycle 1				Cycle 2		⩾Cycle3	EOT [2]	SFU [3]	LTFU[4]
Visit Day	D28~ D-1	D1	D8	D15	D22	D 1	D15	D1			
Evaluation Window (Days)		0	±1	±1	±1	±3	±1	±3	±7	±7	±7
Administrative Procedures											
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics	X										
Medical history	X										
Concurrent diseases	X										
Clinical Procedures/Assessments											
Weight	X	X	X	X	X	X	X	X	X		
Body height	X	X	X	X	X	X	X	X	X		
Physical examination[5]	X	X	X	X	X	X	X	X	X		
vital signs[6]	X	X	X	X	X	X	X	X	X		
ECOG Score	X	X	X	X	X	X	X	X	X		
12-lead ECG[7]	X	X	X	X	X	X	X	X	X		
Echocardiogram	X	X(Every 3weeks)									
Laboratory Assessments											
Blood Chemistry	X	X*	X	X	X	X	X	X	X		
Hematology	X	X*	X	X	X	X	X	X	X		
Coagulation	X	X*	X	X	X	X	X	X	X		
Urinalysis	X	X*	X	X	X	X	X	X	X		
Virology: HBV, HCV, and HIV[8]	X										
Pregnancy[9]	X										
COVID-19[10]	X										
PK Assessments											
PK Blood Samples[11]		X	X	X		X	X	X			
Efficacy Assessments											
Tumor Assessmen[12]	X	X (End of every 8 weeks in the first year; and every 12 weeks thereafter)									
Biomarker Exploration											
18F-FES PET/CT[13]						X					

Items	**Screening[1]**	**Escalation**							**Follow-up**		
		Cycle 1				**Cycle 2**		**⩾Cycle3**	**EOT [2]**	**SFU [3]**	**LTFU[4]**
Visit Day	**D28~ D-1**	**D1**	**D8**	**D15**	**D22**	**D 1**	**D15**	**D1**			
Evaluation Window (Days)		0	±1	±1	±1	±3	±1	±3	±7	±7	±7
Administrative Procedures											
Palbociclib Tablet		Each cycle D1-21 for continuous administration, then D22-28 withdrawal									
FWD1802 Tablet		Continuous Dosing									
Adverse Events	X										
Concomitant Medications and Non-Drug Supportive Interventions	X										

Note: * 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 C1D1. Other examinations may be conducted if deemed clinically necessary by the investigator.

1. Screening assessments are performed within 28 days before C1D1. Screening assessments performed no more than 7 days before C1D1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

2. The end-of-treatment (EOT) will occur at the earliest day possible within 7 days after the last dose of FWD1802 or the subject decides to withdraw from study treatment for any reason.

3. Safety follow-up (SFU) visit should be performed at 28 ±7 days after the last administration and prior to the initiation of a new anti-tumor therapy. Subjects who discontinue the study due to an unacceptable adverse event should be followed until AE relieves to grade 0-1 or AE is stable. If EOT visit is within the safety follow-up window, no further safety follow-up is required.

4. LTFU (long term follow-up) visit is for survival follow-up. LTFU visit will performed every 12(±7) weeks after completion of SFU (phone contact is acceptable if the patient cannot return to the site).

5. Physical examination includes examination of whole human body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, abdomen, back, musculoskeletal, orientating neurologic, and psychiatric systems).

6. Vital signs include temperature, pulse, breathing and blood pressure. On C1D1, C1D8, C1D15, C1D22, C2D1, C2D15 and (C3~Cn) D1, the vital signs will be measured at pre-morning dose(s), and 0.5 h, 2 h, 4 h, 8 h, 12 h and 24 h after the morning dose(s). Other examinations may be conducted if deemed clinically necessary by the investigator.

7. 12-lead ECG will be performed three times at Screening, 30 min, 20 min and 10 min pre-dose and 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h and 24 h post-dose on C1D1, C1D8, C1D15, C1D22, C2D1, C2D15 and (C3~Cn) D1. The 12-lead ECG will be measured at pre-morning dose(s) and 2 h after the morning dose(s). Meanwhile, 12-lead ECG will be performed on prematurely withdrawn. If QTcF > 450 ms (male) or > 470 ms (female), 3 consecutive ECGs should be collected to calculate the mean QTcF value.

8. Human immunodeficiency virus antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and Treponema pallidum antibody. period and may optionally be done at additional time points depending on investigator discretion

9. Only applicable to women of childbearing age; Subjects must have a negative blood pregnancy test during the screening period. Pregnancy tests will be performed anytime during the course of the study, as per investigator's discretion. Serum or urine tests are acceptable based on the site's standard clinical practice, if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

10. Infectious disease screening includes polymerase chain reaction for SARS-CoV-2;.

11. Blood will be collected for PK analysis of the FWD1802 Tablet and/or its metabolites (if any), details please refer to 7.5.1 PK Samples.

14. Tumor assessment: All patients will undergo MRI, chest, abdomen, pelvis and bone examination at baseline period, and subsequent imageological examination included the chest, abdomen, pelvis, and other metastatic sites, if any. The preferred imaging methodology is CT enhanced scan, and using the same imaging examination method and examination conditions before and after the same lesion (including scanning slice thickness, contrast agent, etc.). However, If patient has a contrast allergy or intolerance to contrast medium, a plain CT scan is allowed. 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. Each imaging examination should be performed in accordance with the original imaging schedule, without adjustment due to dose delay. Tumor assessments will continue until disease progression and will not be interrupted due to discontinuation of the study treatment.

- CT/MRI examination in the screening period should be confirmed by the sponsor to be acceptable with the test results before the C0D1 meeting the requirements (including the test results before the subject signs the informed consent form).

- Bone scan should be performed during the screening period. The bone scan during the screening period was performed by the sponsor to confirm the results of the research hospital within 42 days before the C0D1 that could meet the research requirements (including the results of the examination before the subject signed the informed consent). Bone scan was performed only when there were clinical indications during the study period.

- The investigator may perform off-schedule imaging assessment at any time when disease progression is suspected. Subjects with a first CR or PR should be confirmed by imaging confirmation or the next efficacy evaluation after at least 4 weeks..

12. Using 18F-FES PET to monitor the detect in ER target occupation and inhibition.

Table 3 Schedule of Events in Part C Dose Expansion

Items	Screening[1]	Expansion			Follow-up		
		Cycle 1	Cycle 2	⩾Cycle3	EOT [2]	SFU [3]	LTFU[4]
Visit Day	**D28~ D-1**	**D1**	**D 1**	**D1**			
Evaluation Window (Days)		0	±3	±3	±7	±7	±7
Administrative Procedures							
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics	X						
Medical history	X						
Concurrent diseases	X						
Clinical Procedures/Assessments							
Weight	X	X	X	X	X		
Body height	X	X	X	X	X		
Physical examination[5]	X	X	X	X	X		
vital signs[6]	X	X	X	X	X		
ECOG Score	X	X	X	X	X		
12-lead ECG[7]	X	X	X	X	X		
Echocardiogram	X	X(Every 3weeks)					
Laboratory Assessments							
Blood Chemistry	X	X	X	X	X		
Hematology	X	X	X	X	X		
Coagulation	X	X	X	X	X		
Urinalysis	X	X	X	X	X		
Virology: HBV, HCV, and HIV[8]	X						
Pregnancy[9]	X						
COVID-19[10]	X						
PK Assessments							
PK Blood Samples[11]		X	X	X			
Efficacy Assessments							
Tumor Assessmen[12]	X	X (End of every 8 weeks in the first year; and every 12 weeks thereafter)					
Biomarker Exploration							

Items	**Screening**[1]	**Expansion**			**Follow-up**		
		Cycle 1	**Cycle 2**	**⩾Cycle3**	**EOT** [2]	**SFU** [3]	**LTFU**[4]
Visit Day	**D28~ D-1**	**D1**	**D 1**	**D1**			
Evaluation Window (Days)		0	±3	±3	±7	±7	±7
Administrative Procedures							
18F-FES PET/CT[13]	X		X				
FWD1802 Tablet	X	Continuous Dosing					
Adverse Events	X						
Concomitant Medications and Non-Drug Supportive Interventions	X						

Note: * 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.

1. Screening assessments are performed within 28 days before C1D1 dose. Screening assessments performed no more than 7 days before C1D1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

2. The end-of-treatment (EOT) will occur at the earliest day possible within 7 days after the last dose of FWD1802 or the subject decides to withdraw from study treatment for any reason.

3. Safety follow-up (SFU) visit should be performed at 28 ±7 days after the last administration and prior to the initiation of a new anti-tumor therapy. Subjects who discontinue the study due to an unacceptable adverse event should be followed until AE relieves to grade 0-1 or AE is stable. If EOT visit is within the safety follow-up window, no further safety follow-up is required.

4. LTFU (long term follow-up) visit is for survival follow-up. LTFU visit will performed every 12(±7) weeks after completion of SFU (phone contact is acceptable if the patient cannot return to the site).

5. Physical examination includes examination of whole human body systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, abdomen, back, musculoskeletal, orientating neurologic, and psychiatric systems).

6. Vital signs include temperature, pulse, breathing and blood pressure. On C1D1, C2D1 and (C3~Cn) D1, the vital signs will be measured at pre-morning dose(s), and 0.5 h, 2 h, 4 h, 8 h, 12 h and 24 h after the morning dose(s). Other examinations may be conducted if deemed clinically necessary by the investigator.

7. 12-lead ECG will be performed three times at Screening, 30 min, 20 min and 10 min pre-dose and 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h and 24 h post-dose on C1D1, C2D1 and (C3~Cn) D1. The 12-lead ECG will be measured at pre-morning dose(s) and 2 h after the morning dose(s). Meanwhile, 12-lead ECG will be performed on prematurely withdrawn. If QTcF > 450 ms (male) or > 470 ms (female), 3 consecutive ECGs should be collected to calculate the mean QTcF value.

8. Human immunodeficiency virus antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and Treponema pallidum antibody. period and may optionally be done at additional time points depending on investigator discretion

9. Only applicable to women of childbearing age; Subjects must have a negative blood pregnancy test during the screening period. Pregnancy tests will be performed anytime during the course of the study, as per investigator's discretion. Serum or urine tests are acceptable based on the site's standard clinical practice, if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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- CT/MRI examination in the screening period should be confirmed by the sponsor to be acceptable with the test results before the C0D1 meeting the requirements (including the test results before the subject signs the informed consent form).

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- The investigator may perform off-schedule imaging assessment at any time when disease progression is suspected. Subjects with a first CR or PR should be confirmed by imaging confirmation or the next efficacy evaluation after at least 4 weeks.

12. Using 18F-FES PET to monitor the detect in ER target occupation and inhibition

List of Abbreviations and Definitions of Terms

Abbreviation/ Specialist Term	Definition
AE	Adverse event
AUC_{0-t}	Area under the plasma concentration time curve
AUC_{0-inf}	The area under the plasma concentration-time curve from time 0 extrapolated to infinity.
AF1	Activation function 1
CL/F	Apparent clearance
C_{max}	Maximum concentration
CR	Complete response
C_{ave_ss}	Average concentration at steady status
C_{max_ss}	Maximum concentration at steady status
C_{min_ss}	Minimum concentration at steady status
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DBD	DNA binding domain
DCR	Disease control rate
DF	Degree of fluctuation
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER+	Estrogen receptor positive
eCRF	Electronic case report form
GCP	Good Clinical Practice
GGT	Glutamyl transpeptidase
HED	Human equivalent dose
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely toxic dose

Abbreviation/ Specialist Term	Definition
ICH	Ineternational Council for Harmonization of Techincal Requirements for Pharmaceuticals for Human Use
LBD	Ligand binding domain
MAD	Maximum allowable dose
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NMPA	National Medical Products Administration
ORR	Objective response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progress free survival
PK	Pharmacokinetics
PKCS	Pharmacokinetics concentration set
PKPS	Pharmacokinetics parameter set
QD	Once-daily
RP2D	Recommended Phase II dose
SAE	Severe adverse event
SAP	Statistical analysis plan
SD	Stable disease
SERD	Selective estrogen receptor downregulator
SERM	Selective estrogen receptor modulators
SMC	Safety Monitoring Committee
SOC	System Organ Classification
SOP	Standard Operating Procedure
$t_{1/2}$	Elimination half life
TEAE	Treatment emergent adverse event
Tmax	Peak time
UBG	Urobilinogen
ULN	Upper Limits of Normal

Abbreviation/ Specialist Term	Definition
Vd/F	Apparent volume of distribution
Vss	Steady state volume of distribution
λz	Elimination rate constant

1 Introduction

1.1 Background

Breast cancer is a cancer that starts in breast tissue. It happens when cells in the breast change and grow out of control. The cells usually form a tumor. In 2020, breast cancer became the most commonly diagnosed cancer type in the world; there were more than 2.26 million new cases of breast cancer and almost 685 000 deaths from breast cancer worldwide. Breast cancer was the most common cause of cancer death in women and the fifth most common cause of cancer death overall(Organization). Approximately 70% of breast cancers are estrogen receptor positive (ER+) and are classified as luminal A or luminal B subtype (Lu & Liu, 2020).

Treatment strategies differ according to molecular subtype. Management of breast cancer is multidisciplinary; it includes locoregional (surgery and radiation therapy) and systemic therapy approaches. Systemic therapies include endocrine therapy for hormone receptor-positive disease, chemotherapy, anti-HER2 therapy for HER2-positive disease, bone stabilizing agents, poly(ADP-ribose) polymerase inhibitors for BRCA mutation carriers and, quite recently, immunotherapy(Harbeck et al., 2019).

Early stage ER+ breast cancer is usually treated with surgery; in contrast, advanced stage breast cancer is commonly associated with metastasis to distant organs and surgical treatment is generally no longer an option (Maughan, Lutterbie, & Ham, 2010; Osborne, 1998). Endocrine therapy (ET) is the first-line treatment available for ER+ breast cancer patients and the available drugs are categorized into three major types: selective estrogen receptor modulators (SERMs), aromatase inhibitors or SERDs (Lu & Liu, 2020; Shagufta, Ahmad, Mathew, & Rahman, 2020). SERMs compete with estrogen for ER binding and show mixed agonist/antagonist capabilities in a tissue-specific fashion (Liu, Han, & Smith, 2013). Aromatase is an enzyme that plays a significant role in the biosynthesis of important endogenous estrogens from androgens. Aromatase inhibitors such as anastrozole are compounds that are competitive inhibitors of the enzyme aromatase and block the synthesis of estrogen by binding to the estrogen receptor (Ahmad & Shagufta, 2015; Ravisekar, 2007). SERDs create an unstable protein complex that induces ER protein degradation via proteasome (Liu et al., 2013).

Unfortunately, 30−50% of ER positive tumors become resistant to SERM/AI treatment after 3−5 years (Lu & Liu, 2020). Clinical resistance associated with progression of disease remains a significant therapeutic challenge. Mutations of the ESR1 gene, which encodes the ER, have been increasingly recognized as an important mechanism of ET resistance, with a prevalence that ranges from 11 to 39% (Reinert, Saad, Barrios, & Bines, 2017). Targeted therapy directed to ESR1-mutated clones is an appealing concept, and preclinical and clinical development of rationale-based novel therapeutic strategies, new-generation SERDs that inhibit these ER mutants has the potential to substantially improve treatment outcomes (Reinert et al., 2017). Based on current research (Fribbens et al., 2016), ESR1 mutations are associated with inferior outcomes with further AI treatment and ESR1-mutant cancers show selective sensitivity to fulvestrant, the only approved SERD.

Direct targeting of ERα is achieved by selective estrogen receptor modulator (SERM) (e.g., tamoxifen) and selective estrogen receptor degrader (SERD) (e.g., fulvestrant). SERMs compete with estrogen for ER binding and show mixed agonist/antagonist capabilities in a tissue-specific fashion. Meanwhile, SERDs create an unstable protein complex that induces ER protein degradation via proteasome (Liu et al., 2013). SERDs are therefore considered a significant therapeutic approach to treat ER+ BC in both early stage and more advanced drug-resistant cases. These types of treatment have demonstrated to improve both survival and relapsing times.

Fulvestrant is currently an important therapeutic approach for the treatment of endocrine-resistant breast cancers. The poor pharmacokinetic properties of fulvestrant have inspired the development of a new generation of oral SERDs to overcome the poor pharmacokinetic and drug resistance (Hernando et al., 2021).

FWD1802 is a novel oral SERD, which binds competitively to the ER, with an affinity approximately comparable to that of fulvestrant. FWD1802 acts as a competitive inhibitor of the activation of the ER by estradiol, causing the ER to be degraded and thus downregulated. In vitro, anti-proliferative effects studies have demonstrated that FWD1802 showed a significant growth inhibitory effect in all 3 ER-positive human breast cancer cell lines (MCF7, T47D, CAMA1) and 2 MCF7 cell lines with ERα Y537S or D538G mutation (MCF7/ERα Y537S and MCF7/ERα D538G) with the relative IC50 values from 0.0005 μM to 0.0248 μM. Also, FWD1802 exhibits anti-tumor activity in the ER-positive or ESR1 Y537S mutation human breast cancer xenograft models. Besides, the combination of FWD1802 and Palbociclib significantly inhibited tumor growth with greater potency than monotherapy at the same dosage. These results suggest that FWD1802 has the potential to provide clinical benefit to ER+ /HER2- unresectable locally advanced or metastatic breast cancer patients and ER+/HER2- unresectable locally advanced or metastatic breast cancer with ESR1 mutation patients as monotherapy and combination.

1.2 Non-Clinical Information

1.2.1 Pharmacology

FWD1802 exhibited significant antagonistic activity against ERα, ERβ, ERα D538G, and ERα Y537S in a concentration-dependent manner. FWD1802 exhibited great ERα degradation potency and efficiency. FWD1802 had no effect on inducing PR expression but significantly down-regulated PR (used as a downstream biomarker of a functional ERα signaling pathway) expression in the presence of estradiol.

In vitro pharmacodynamic studies showed that FWD1802 had significant growth inhibitory effects in ER positive human breast cancer cell lines and genetically engineered MCF7 cell lines with ERα Y537S or D538G mutation.

In vivo, FWD1802 (at the dosage ≥1mg/kg) exhibited anti-tumor activity in the ER-positive or ESR1 Y537S mutation human breast cancer xenograft models. Besides, the combination of FWD1802 and Palbociclib significantly inhibited tumor growth with greater potency than monotherapy at the same dosage.

The in vitro target screening studies showed that there was a low off-target potential of the FWD1802. However, because the clinical C_{max} cannot be obtained until the phase 1 clinical trials, the safety of the compound needs to be further verified by future data.

There were no test article-related adverse effects on the CNS, respiratory and cardiovascular systems. The IC50 for the inhibitory effect of FWD1802 on hERG potassium current was 4.51 μM. The safety of the compound on cardiovascular needs to be further verified by actual clinical exposure.

1.2.2 Pharmacokinetics

FWD1802 demonstrated low permeability across the Caco-2 cell monolayer. The systemic exposure of FWD1802 increased dose proportionally with the dose levels and no marked accumulation was observed post repeated oral dosing in rats and dogs. FWD1802 showed no sex differences at all dose levels when comparing the AUC0-last and Cmax in male and female rats or dogs. The systemic exposure of FWD1802-IM02 was relatively stable compared to FWD1802, and the two isomers (FWD1802-IM02 and FWD1802) exist as a relatively fixed ratio in rats and dogs, with the AUC Ratio values 0.0866~0.121 and 0.0958 to 0.120, and the Cmax Ratio values 0.0941~0.126 and 0.0793 to 0.105, respectively in all PO dose groups. In addition, the same or similar mean PK parameter values for the two isomers were observed, including T_{max}, $T_{1/2}$, and so on. Overall, there is the reason to consider that the two isomers have same or similar pharmacokinetic behavior in male and female SD rats/beagle dogs.

The binding of FWD1802 to plasma protein were high in rat, monkey and human (>95%), very high in dog (>99%), or high to very high in mouse (>98%). Following a single oral dose of [^{14}C] FWD1802 at 10 mg/100 μCi/kg to intact rats, FWD1802 distributed widely and mainly distributed in lungs, liver, stomach wall and intestine tract wall. The peak concentrations of TRA was reached in 4 h post-dose in most tissues and blood. At 72 h post-dose, the TRA in blood and brain of male and female rats, and heart of female rats were below the limit of quantitation, the TRA in blood and other tissues were all still detected measurable concentrations. The TRA exposure (C_{max}) in reproductive organ of female rats were significantly higher than those of male rats, while the exposure levels in other tissues were similar between male and female rats.

FWD1802 was moderately metabolized in SD rat, cynomolgus monkey and human liver microsomes, and slowly metabolized in CD-1 mouse and beagle dog liver microsomes. Meanwhile, FWD1802 was highly metabolized in CD-1 mouse, SD rat, and beagle dog hepatocytes, moderately metabolized in cynomolgus monkey and human hepatocytes. But there was no significant difference in the peak area ratio of FWD1802-IM02 to FWD1802 in different species liver microsomes or hepatocytes and incubation time. FWD1802 was stable in whole blood of different species, SGF within 6 hours, and SIF within 24 hours. And there was no significant difference in the peak area ratio of FWD1802-IM02 to FWD1802 in blood, SGF or SIF. FWD1802 was mainly unchanged in liver microsomes, primarily metabolized via N-dealkylation, mono-oxygenation, hydrolysis, and dedecarboxylation. The metabolites formed in the incubation of human liver microsomes were detected in microsomes of at least one of the animal species. In the mouse, rat, dog,

monkey, and human hepatocytes, in addition to the unchanged FWD1802, a total of 14 metabolites of FWD1802 were detected and identified. FWD1802 was mainly metabolized via glucuronidation and N-dealkylation. M8 (glucuronidation metabolites) was the metabolite only detected in human hepatocytes, accounting for 0.95%. The no detection of M8 in animal species might be caused by less metabolism extent in animal species. CYP3A was the major metabolic enzyme responsible for the formation of metabolites from FWD1802. Based on the metabolites of [^{14}C] FWD1802 identified in SD rat blood, bile, urine and feces, the major metabolic clearance pathways of [^{14}C] FWD1802 were 1) dehydrogenation to form M1, M2 and M15, excreted from feces via bile; 2) N-dealkylated to form M14, or glucuronidation to form M7, mainly excreted from feces via bile; 3) unchanged drug directly excreted from feces. The major metabolic pathway of FWD1802 in beagle dogs blood was oxidative defluorination.

The excretion route of FWD1802 was mainly via feces, and the excretion rate and recovery from male and female rats were similar.

FWD1802 revealed inhibition CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, while no inhibitory effects on CYP1A2. FWD1802 showed no time-dependent inhibition on CYP1A2, CYP2B6 and CYP2D6, but it showed time-dependent inhibition on CYP2C8, CYP2C9, CYP2C19 and CYP3A. FWD1802 might be an inducer for CYP3A4 or CYP2B6, but had no induction potential on CYP1A2. And, FWD1802 inhibited efflux mediated by P-glycoprotein and BCRP. It was probably a P gp substrate but a poor or non-BCRP substrate. Besides, FWD1802 demonstrated inhibition on OATP1B1, OATP1B3, OAT1, OCT2, MATE1, or MATE2-K except OAT3. In addition, FWD1802 was not a substrate for OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K transporter.

1.2.3 Toxicology

For safety evaluation, the MTDs from GLP-compliant single-dose oral toxicity studies were 400 or 200 mg/kg for male or female rats, respectively, and 200 mg/kg for dogs. Two 28-day repeated dose toxicity studies were conducted in rats and dogs. The STD10 in rats was considered to be 26 mg/kg/day and the HNSTD in dogs was 15 mg/kg/day.

FWD1802 when administered once daily for 28 days to rats was well tolerated. Test article-related adverse changes were limited to decreased food consumption and body weight gain in males at 26 mg/kg/day, and anatomic findings within ovaries and uterus in females at ≥6.5 mg/kg/day which were attributed to the intended pharmacology (selective estrogen receptor degrader) of the test article. Test article-related adverse changes in dogs were limited to histopathological findings in the reproductive tract in both sexes at ≥2.5 mg/kg/day.

In vitro genotoxicity studies showed there was no genotoxicity risk for FWD1802.

In summary, FWD1802 displayed a high degree of selectivity to ER, causing the ER to be degraded and thus downregulated. FWD1802 showed a significant growth inhibitory effect in ER-positive human breast cancer cell lines and MCF7 cell lines with ERα Y537S or

D538G mutation. FWD1802 monotherapy or combination with Palbociclib exhibit desired anti-tumor activity in the ER-positive or ESR1 Y537S mutation human breast cancer xenograft models. Besides, the potential toxicity of FWD1802 was well assessed in nonclinical safety assessments, and the results support the proposed phase 1 clinical trial with appropriate monitoring.

1.3 Study Rationale

1.3.1 Rational for Dose Regimen of Escalation

The starting dose in humans is mainly determined based on the nonclinical information. It is based on the ICH guidance which recommends that the starting dose should be either 1/10 of the severely toxic dose occurring in 10% of animals in rodent toxicity studies (STD10) or 1/6 of the highest non-seriously toxic dose (HNSTD) observed in non-rodent studies.

The HNSTD was determined to be 15 mg/kg/day in dogs from the repeated toxicity study. Converting from animal dose to human dose normalized by body surface area, the human equivalent dose (HED) derived from 1/6 of the dog HNSTD is calculated to be 81 mg/day.

The STD10 was determined to be 26 mg/kg/day in rats from the repeated toxicity study. Converting from animal dose to human dose normalized by body surface area, the human equivalent dose (HED) derived from 1/10 of the rat STD10 is calculated to be 25 mg/day. The conversion is provided in Table 4.

Table 4 tarting Dose for Escalation

	Animal	Dose	HED	MRSDa
Toxicity	Rats	26 mg/kg/day	0.42 mg/kg/day	25 mg/day
-	Dogs	15 mg/kg/day	1.35 mg/kg/day	81 mg/day

a: calculated based on human body weight of 60 kg.

For the time being, the proposed starting dose 25 mg/day is considered to be a safe dose for administration to ER+/HER2- unresectable locally advanced or metastatic breast cancer patients. The proposed maximum dose in humans has been provisionally set as 450 mg/day; it may be adjusted based on the tolerability of the previous dose level (Part A).

1.4 Benefits and Risks

1.4.1 Possible adverse events

- Nonclinical Toxicology

In the 28-day repeat-dose toxicity study conducted in SD rats: test article-related changes in food consumption and body weights were noted in all treatment groups. In dosing phase, food consumption decreased in males (up to 17.6%) and increased in females (up to 19.2%) at ≥6.5 mg/kg/day, when compared with the control group. This reflected in the body

weight gain in dosing phase, with a slight decrease in males whereas a slight increase in females. As a result, at the end of dosing phase, mean body weights decreased by 12.03-15.13% in males and increased by 19.96-22.17% in females at ≥6.5 mg/kg/day, when compared with the control group. The difference between males and females were attributed to the intended pharmacology (selective estrogen receptor degrader) of the test article. Following a 4-week recovery, the changes in food consumption and body weight gain had a tread of recovery in males at doses of 6.5 and 13 mg/kg/day and females at ≥6.5 mg/kg/day, indicating reversibility in these groups. In contrast to this, changes in males at 26 mg/kg/day showed no signs of recovery, and, thus, were considered adverse. Therefore, during clinical trials, the body weight of subjects shall be monitored.

In the 28-day repeat-dose toxicity study conducted in SD rats: at the end of dosing phase, test article-related hematology changes were seen in females at ≥6.5 mg/kg/day and limited to increased reticulocyte (up to 35.8%) and corresponding increase in red blood cell width at ≥6.5 mg/kg/day, increases in neutrophils (up to 71.67%), lymphocytes (up to 77.64%), monocytes (up to 98.21%), basophils (up to 150%) and total number of leukocytes at ≥6.5 mg/kg/day, and increased eosinophils (up to 81.25%) at ≥13 mg/kg/day, when compared with the control group. These changes were reversible not being present at the end of recovery phase, and lacked correlates in pathology findings, therefore were considered non-adverse. Additionally, there were slight increases in erythrocyte, hemoglobin and hematocrit at the end of recovery phase, which were considered secondary to the reticulocyte increase in dosing phase. Therefore, during clinical trials, the serum biochemistry parameters, hematology parameters and any other adverse reactions of subjects shall also be concerned.

In the 28-day repeat-dose toxicity study conducted in beagle dogs: test article-related ophthalmic finding were noted in both sexes at 15 mg/kg/day including bilateral conjunctiva hyperemia and/or ocular discharge. The ocular discharge was also noted in the clinical observations in both sexes at 15 mg/kg/day with higher incidence and the number of animals affected than control group. These signs were recoverable during the recovery phase. Therefore, during clinical trials, the physical examination should be performed regularly to monitor the subject's eye examination..

- Clinical Adverse Effects of FASLODEX® (Fulvestrant)

As a similar-targeted drug, Fulvestrant is an approved SERD for the treatment of endocrine-resistant breast cancers. 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.

Comparison of FASLODEX 500 mg and FASLODEX 250 mg (CONFIRM)(FDA, 2021)

The following adverse reactions (Nevens et al.) were calculated based on the safety analysis of CONFIRM comparing the administration of FASLODEX 500 mg intramuscularly once

a month with FASLODEX 250 mg intramuscularly once a month. The most frequently reported adverse reactions in the FASLODEX 500 mg group were injection site pain (11.6% of patients), nausea (9.7% of patients), and bone pain (9.4% of patients); the most frequently reported adverse reactions in the FASLODEX 250 mg group were nausea (13.6% of patients), back pain (10.7% of patients), and injection site pain (9.1% of patients).

Table 5 lists adverse reactions reported with an incidence of 5% or greater, regardless of assessed causality, from CONFIRM.

Table 5 Adverse Reactions in CONFIRM (≥5% in Either Treatment Group)

Adverse Reactions	FASLODEX 500 mg N=361 %	FASLODEX 250 mg N=374 %
Body as a Whole		
Injection Site Pain1	12	9
Headache	8	7
Back Pain	8	11
Fatigue	8	6
Pain in Extremity	7	7
Asthenia	6	6
Vascular System		
Hot Flash	7	6
Digestive System		
Nausea	10	14
Vomiting	6	6
Anorexia	6	4
Constipation	5	4
Musculoskeletal System		
Bone Pain	9	8
Arthralgia	8	8
Musculoskeletal Pain	6	3
Respiratory System		
Cough	5	5
Dyspnea	4	5

1Including more severe injection site related sciatica, neuralgia, neuropathic pain, and peripheral neuropathy.

In the pooled safety population (N=1127) from clinical trials comparing FASLODEX 500 mg to FASLODEX 250 mg, post-baseline increases of ≥1 CTC grade in either AST, ALT, or alkaline phosphatase were observed in >15% of patients receiving FASLODEX. Grade 3-4 increases were observed in 1-2% of patients. The incidence and severity of increased hepatic enzymes (ALT, AST, ALP) did not differ between the 250 mg and the 500 mg FASLODEX arms.

Combination Therapy with Palbociclib (PALOMA-3)(FDA, 2021)

The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8

months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving FASLODEX plus palbociclib, and in 6 of 172 (3%) patients receiving FASLODEX plus placebo. Adverse reactions leading to discontinuation for those patients receiving FASLODEX pluspalbociclib included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions (⩾10%) of any grade reported in patients in the FASLODEX plus palbociclib arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade ⩾3 adverse reactions (⩾5%) in patients receiving FASLODEX plus palbociclib in descending frequency were neutropenia and leukopenia.

Adverse reactions (⩾10%) reported in patients who received FASLODEX plus palbociclib or FASLODEX plus placebo in PALOMA-3 are listed in Table 6, and laboratory abnormalities are listed in Table 7.

Table 6 Adverse Reactions (≥10%) in PALOMA-3

Adverse Reactions	FASLODEX plus Palbociclib N=345			FASLODEX plus Placebo N=172		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and Infestations						
Infections1	472	3	1	31	3	0
Blood and Lymphatic System Disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal Disorders						
Nausea	34	0	0	28	1	0
Stomatitis3	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	184	N/A	N/A	65	N/A	N/A
Rash6	17	1	0	6	0	0
General Disorders and Administration Site Conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

1 Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

2 Most common infections (⩾1%)include: nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, bronchitis, rhinitis, conjunctivitis, pneumonia, sinusitis, cystitis, oral herpes,

respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, paronychia.
3 Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
4 Grade 1 events – 17%; Grade 2 events – 1%.
5 Grade 1 events – 6%.
6 Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving FASLODEX plus palbociclib in PALOMA-3 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Table 7 Laboratory Abnormalities in PALOMA-3

Laboratory Parameters	FASLODEX plus Palbociclib N=345			FASLODEX plus Placebo N=172		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

1.4.2 Risk control in trial design

In the clinical study, a series of examinations (exams) at the screening and treatment period will be conducted. The frequency of the clinical laboratory (lab) tests such as blood biochemistry will be increased accordingly, if needed. Additional tests may be added, if deemed necessary. Additional risk to subjects include those attributable to study participation in general, including risks associated with frequent medical tests and laboratory blood draws, and the associated pain and discomfort.

Strategies to mitigate these risks include close monitoring of adverse events (AEs) and lab results. Both individual and trial stopping criteria will be specified, AEs will be assessed in this protocol, and AEs of special interest will be paid extra attention. Supportive care and risk control management will also be provided to subjects, including appropriate treatment of any AEs. The risk to participants in this trial will be minimized by adherence to the eligibility criteria, closely clinical monitoring and stopping rules.

Overall, the nonclinical data showed a positive benefit/risk ratio to support the clinical development of FWD1802 with appropriate safety monitoring. Data obtained from this

study will be provided to support later stages of clinical development for FWD1802 to be conducted in selected populations.

1.5 Clinical Study Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements in United States

2 Objectives

Primary Objective:

- Establish the recommended phase II dose (RP2D) and/or the maximum tolerated dose (MTD) of FWD1802 as monotherapy and in combination with palbociclib in patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer
- Explore the safety and tolerability of FWD1802 as monotherapy and in combination with Palbociclib

Secondary Objective:

- Characterise Pharmacokinetics of FWD1802 as monotherapy and in combination with palbociclib
- Explore preliminary efficacy signals

Exploratory Objective:

- Biomarker of FWD1802 as monotherapy and in combination with palbociclib

3 Endpoints

Safety should be evaluated at follow-up visits and throughout the study. Adverse events will be assessed for their severity (based on the NCI-CTCAE 5.0 rating), duration, and association with study treatment.

The following safety indicators will be measured and evaluated at designated intervals throughout the study. Patient history was taken at baseline to understand underlying conditions.

3.1 Safety and Tolerability

- Incidence of DLT in the MTD evaluation period, adverse events, treatment emergent adverse event (TEAE), serious adverse event (SAE), their relationship with the investigational product and respective severity.

- Changes in vital signs, ECOG score, ECG, physical examination, and laboratory tests before and after treatment, and the use of concomitant medication.

3.2 PK Assessment

- Maximum plasma concentration (C_{max}), Time to C_{max} (T_{max}), Area under the concentration versus time curve from time 0 to the last measurable concentration (AUC_{0-t}), The area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC_{0-inf}); if data permitted, elimination half-life time ($t_{1/2}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F), and elimination rate constant (λz);

- Minimum concentration at steady state (C_{min_ss}), Maximum concentration at steady state (C_{max_ss}), Average concentration at steady state (C_{ave_ss}), $t_{1/2}$, CL/F, AUC_{tau_ss}, Volume at steady state (V_{ss}), elimination rate Constant (λz), accumulation ratio (AR) based on C_{max} and AUC_{tau_ss};

3.3 Efficacy Assessment

- Tumor response assessments by the corresponding criteria by RECIST v1.1 to assess Objective response rate (ORR), Clinical benefit rate (CBR), Duration of response (DoR), and Disease control rate (DCR) after the study treatment.

3.4 Exploratory endpoints

- The correlation between ER target inhibition by using [^{18}F]-fluorestradiol (FES) PET/CT and efficacy.

- Progression free survival (PFS) and Overall survival (OS).

- Other potential biomarker as needed.

4 Investigational Plan

4.1 Overall Study Design

This study is a multicenter, open-label, first-in-human study evaluating FWD1802 in patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer . It includes three parts: the dose escalation of FWD1802 as a monotherapy study (Part A), the dose escalation of FWD1802 in combination with palbocilib study (Part B) and the dose expansion of FWD1802 as a monotherapy study in ESR1 mutation patients. (Part C).Part A: Dose Escalation: It aims to investigate the safety, tolerability, PK, PD, and preliminary efficacy in patients with ER+ /HER2- unresectable locally advanced or metastatic breast cancer who have failed or are intolerant of standard treatment, or have no standard therapy.

Part B: Dose Escalation: It aims to investigate the safety, tolerability, PK, PD, and preliminary efficacy in patients with ER+ /HER2- unresectable locally advanced or metastatic breast cancer who have failed or are intolerant of standard treatment, or have no standard therapy.

Part C: Dose Expansion: It aims to further evaluate the safety, tolerability, PK, PD, and preliminary efficacy of FWD1802 in approximately 60 eligible subjects with ER+ /HER2- unresectable locally advanced or metastatic breast cancer with ESR1 mutation under the dose level of the recommended dose for expansion(s) identified in part A study.

The overall study design is presented graphically in Figure 1. The detailed study procedures are provided in Section 7

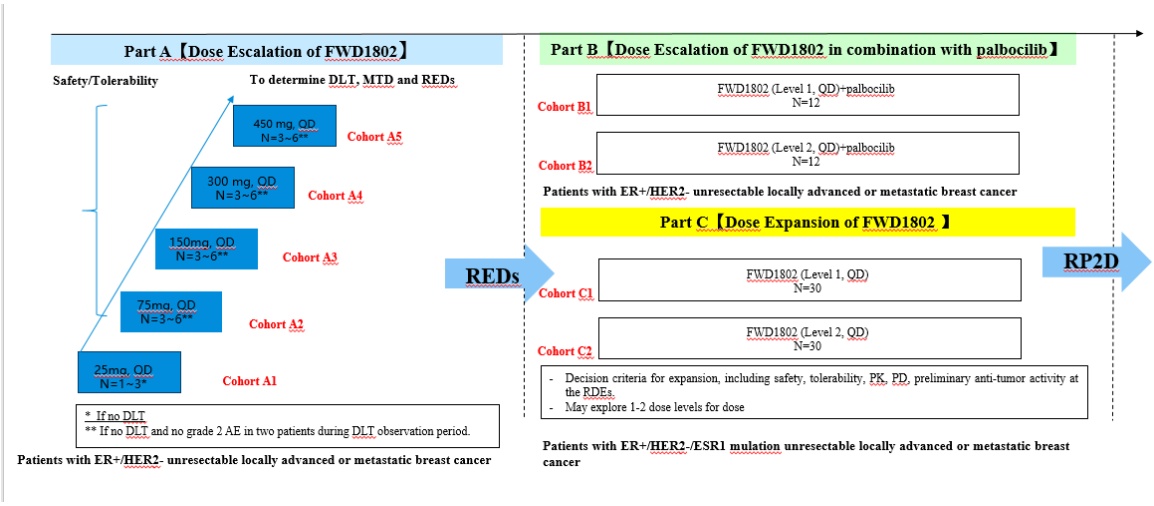

Figure 1 Clinical Design of FWD1802 in Phase I Trial

4.2 Methodology

4.2.1 Part A – Dose Escalation of FWD1802 as a Monotherapy

Part A study will be conducted in subjects diagnosed with ER+/HER2- unresectable locally advanced or metastatic breast cancer, to evaluate the safety and tolerability, PK, PD and preliminary anti-tumor activity of FWD1802 Tablet, and to determine RDEs. A maximum of 27 subjects will be enrolled. They will be sequentially allocated to 5 planned dose cohorts: 25 mg, 75 mg, 150 mg, 300 mg and 450 mg.

Subjects enrolled will be orally administered a single dose of FWD1802 Tablet on Cycle 0 Day 1 (C0D1), followed by a 5-day observation period to evaluate the PK and safety of the drug product. Starting on Cycle 1 Day 1 (C1D1), FWD1802 Tablet will be orally administered continuously once or quaque die (QD) for 28 consecutive days of each cycle. The DLT observation period is set as 34 days after the initial administration (1 cycle) (single-dose period and the first 28-day cycle). The second cycle and subsequent cycles will last for 28 days per cycle. The patients will continue to receive the study treatment until disease progression, death, unacceptable toxicity, withdrawal of informed consent, or other reasons to discontinue study treatment occurs, whichever comes first.

Part A will utilize an accelerated dose escalation design to enroll one patient to dose levels 1, which will be converted to a traditional '3+3' design when a grade 2 or higher toxicity occurs during cycle 1 therapy at these dose levels unless it is clearly related to disease progression or extraneous cause, whichever comes first.

Before starting the next dose level, all subjects (n=1, 3, or 6) at the current dose level must complete the DLT observation period. The Safety Monitoring Committee (SMC) will decide whether the study will proceed to the next dose level. Please refer to Section 4.7 Dose modifications.

Based on the safety data, a higher dose level beyond dose level 5 or an intermediate dose level can be explored as determined by the SMC.

The planned escalation dose levels are shown below:

Table 8. The Planned Dose Escalation Levels of FWD1802 in Phase Ia Study

Groups	Dose (mg) *	Percentage of escalation (%)	Number of subjects
1(Starting dose)	25	/	1~3
2**	75	200%	3~6
3**	150	100%	3~6
4**	300	100%	3~6
5**	450	50%	3~6

**Dose levels will be determined based on the results of lower doses, at the discretion of SMC.

4.2.2 Part B- Dose Escalation of FWD1802 in combination with palbocilib

The dose expansion study will be conducted in approximately 24 eligible subjects diagnosed with ER+/HER2- unresectable locally advanced or metastatic breast cancer, to

evaluate the safety, tolerability, PK, PD, and preliminary efficacy of FWD1802 in combination with palbocilib.

The starting dose level for Part B study will be determined by SMC based on safety data (including the AE rate of non-DLT), PK, PD and preliminary efficacy in Part A. Every treatment cycle consists of 28 days.

In brief, based on the available data obtained from Part A, 1 to 2 dose levels may be selected as the recommended dose levels (RDs) to evaluate FWD1802 in combination with palbocilib in these patients.

4.2.3 Part C – Dose Expansion Study

Part C (Dose Expansion of FWD1802 as a Monotherapy) can be conducted in parallel with Part A (Dose Escalation of FWD1802 as a Monotherapy) provided that the following two conditions are met:

a) The starting dose of Part C study should be lower than the dose of monotherapy RP2D or the dose that has been explored and confirmed as safe for monotherapy.

b) The SMC will review all available PK, PD, safety, tolerability and efficacy data for Part A study and decide whether the study may proceed to Part C portions.

The dose expansion study will be conducted in approximately 60 eligible subjects diagnosed with ER+/HER2-/ESR1 mutation unresectable locally advanced or metastatic breast cancer, to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of FWD1802 Tablet at the recommended 1~2 dose level(s) for expansion.

The specific number of subjects, administration dose and dosing regimen in dose expansion study will be determined by SMC based on the results of Part A study.

4.3 Treatment Plan

Subjects will receive FWD1802 tablets orally according to the overall study design; the administration scheme is shown above. Subjects will continue to receive FWD1802 until any of the criteria specified in Section 5.4 Subjects Withdrawal Criteria are met.

Study drugs will be orally administered at the investigational site by site staff at 8 AM on the morning of the dosing days.

Note:the first group of FWD1802 in phase A study (25 mg) will be conducted on the preset conditions, while the dose levels, dosing schedule and biological sample collection time points for other groups might be modified upon emerging data in this study.

4.4 Dose Escalation/Stopping Criteria

The combination of ‘accelerated escalation’ and the traditional ‘3+3’ was used for Part A study. It’s planned that one eligible subject will be enrolled for the evaluation of the first

dose levels (25 mg) using intra-individual dose escalation, when it is approved by sponsor and investigator. If no ≥ grade 2 adverse event (defined as any ≥ grade 2 adverse event occurs during the DLT observation period unless it is clearly related to disease progression or extraneous cause) occurs during the DLT observation period, dose escalation enters the 2nd dose group with the traditional '3+3' mode. Otherwise, additional 2 subjects will be added to the current dose group, and the dose group and subsequent dose groups will switch to a '3+3' dose escalation design. Before starting the next dose level, all subjects (n=1, 3, or 6) at the current dose level must complete the DLT observation period and be determined by the Safety Monitoring Committee (SMC) to proceed to the next dose level. If no DLT has occurred at the end of the DLT observation period, subjects may adjust its dose level to any higher dose level that no DLT events have occurred during the DLT observation period, as assessed by the investigator and determined by the SMC, and on the condition that the investigator considers safe for the subjects.

If MTD cannot be determined at this part due to too few DLT events, a higher dose or an intermediate dose can be explored as needed, after the dose escalation reaches the highest predicted dose or is determined by the SMC.

The traditional '3+3' increment rule for dose escalation is as follows:

- The dose will be escalated if no DLT has been reported in the first 3 subjects of this dose group after DLT observation period.

- If 1 of the first 3 subjects enrolled has DLT occurred, then 3 additional subjects will be enrolled, with totally 6 subjects in this dose group.

  -If only 1 DLT event occurs in these 6 subjects, then the dose will be escalated.

  -If ≥ 2 DLT events occur in these 6 subjects, then no more subjects will be enrolled in this dose group and the dose escalation will be stopped. The SMC will decide whether to use the intermediate dose as the next dose level for the study or to terminate the dose escalation.

- If ≥ 2 DLT events occur in the first 3 subjects, then the dose escalation will be stopped, an intermediate dose or a lower dose level determined by the SMC will be selected as the next dose level for the study; or the dose escalation is terminated, according to the safety results of the enrolled subjects.

4.5 Definition of MTD

- The maximum tolerable dose (MTD) is defined as the highest dose level while the incidence of DLT is less than 33% in the dose escalation study during the DLT evaluation period.

- Six patients are required to establish the MTD. If only 3 patients have been evaluated in the previous dose level below the non-tolerated dose, the cohort should be expanded to 6 patients at the previous dose level below the non-tolerated dose. If DLT is not observed in the additional 3 patients, or 6 patients have been evaluated at the previous

dose level, the MTD will be confirmed at the previous dose level below the non-tolerated dose.

- If MTD is not established at the end of escalation, the maximum safety dose will be defined as the maximum administrated dose (MAD).

- The recommended dose for expansion(s) will be confirmed comprehensively based on the results of safety, tolerability, PK and PD. The RP2D should be a pharmacologically active dose and the dose should be selected by pooling and evaluating all available PK, PD, target engagement, efficacy, safety, and tolerability data to select the appropriate dose. There will need to be at least 6 patients at the recommended dose for expansion level(s) to evaluate the safety, PK, PD and tolerability. If the DLT does not occur during the DLT assessment period, the current highest dose level will not be considered as the basis of dose escalation and may be used as a reference to dose design and safety evaluation of the recommend dose.

Based on the safety data, a higher dose level beyond dose level 9 or an intermediate dose level can be explored as determined by the SMC.

4.6 Definitions of Dose-Limiting Toxicity (DLT)

All AEs of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

1. Hematological toxicity:

- CTCAE Grade ≥4 thrombocytopenia;

- CTCAE Grade 4 neutropenia lasting >7 days;

- CTCAE Grade ≥3 febrile neutropenia, where Grade 3 febrile neutropenia is defined as ANC <1000/mm3 and a single temperature of >38.3° C (101° F) or a sustained temperature of ≥38° C (100° F) for more than one hour;

- CTCAE Grade 3 thrombocytopenia (≥25,000/mm3 and <50,000/mm3) associated with bleeding;

- CTCAE Grade 4 (<25,000/m3) thrombocytopenia lasting>5days;

2. Non-hematological toxicity:

- Hy's law, defined as:

  ✧ AST or ALT > 3 x the upper limit of normal (ULN) AND

  ✧ Total bilirubin > 2 x ULN AND

  ✧ Alkaline phosphatase < 2 x ULN AND

- ✧ No other reason for liver injury

- ALT or AST >8x ULN, ALT or AST >5x ULN for more than 2 weeks, ALT or AST >3x ULN and (TBL >2x ULN or INR >1.5)

  - ✧ For patients with hepatic metastases, AST or ALT > 8 x ULN or AST or ALT > 5 x ULN for ≥ 14 days

- Grade > 3 non-hematologic toxicity with the exception of the following

  - ✧ Grade 3+ fatigue ≥7 days regardless of baseline Grade；

  - ✧ Grade 3 nausea and vomiting, lasting ≤ 2 days with optimal medical management；

  - ✧ Grade 3 diarrhea lasting ≤ 3 days with optimal medical management

  - ✧ ≥3+ non-hematologic abnormalities should also include laboratory values that cause symptoms.

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4.7 Dose modifications

4.7.1 Dose Reductions

Dose reductions will be only allowed beyond DLT evaluation period in the dose escalation and expansion studies. Subjects who experience the unacceptable adverse events may continue treatment at the next lower dose level until disease progression or unacceptable toxicity. Adverse events considered for dose reduction should not include the events assessed by the investigator as exclusively related to underlying disease or other medical condition or concomitant treatment. The dose reduction guideline for general adverse events are outlined in Table 9. Provisions are not made for dose levels below 25 mg. If 25 mg once daily is determined to be unsuitable based on DLT as defined above, FWD1802will be permanently discontinued.

Table 9 Dose reductions guideline for general adverse events

CTCAE grade	Follow-up procedures and dose reductions
CTCAE grade 1	Continue to receive study treatment at same dose level Monitor closely. Provide supportive therapy.
CTCAE grade 2	Discontinue study treatment if there are clinical symptoms. Monitor closely. Provide supportive therapy. Restart study treatment at the same dose level if resolved to CTCAE grade 1 or baseline within 14 days.
CTCAE grade 3	Discontinue study treatment if there are clinical symptoms. Monitor closely.

CTCAE grade	Follow-up procedures and dose reductions
	Provide supportive therapy. Restart to study treatment at one dose level lower (except dose group 1) if resolved to CTCAE grade 1 or baseline. Discontinue treatment if CTCAE grade 3 AE occurs again. Restart to study treatment at one dose level lower if resolved to CTCAE grade 1 orbaseline within 21 days.
CTCAE grade 4	Discontinue study treatment if there are clinical symptoms. Monitor closely. Provide supportive therapy. Restart to study treatment at one dose level lower (except dose group 1) if resolved to CTCAE grade 1 or baseline within 21 days. If CTCAE grade 4 AE occurs again, discontinue permanently based on investigator and sponsor's judgement.

4.7.2 Dose Escalations

Part A will utilize an accelerated dose escalation design to enroll one patient to dose levels 1, which will be converted to a traditional 3+3 design when a grade 2 or higher toxicity occurs during cycle 1 therapy at these dose levels unless it is clearly related to disease progression or extraneous cause, whichever comes first. Intra-individual dose escalation will be allowed in this part A study when it is approved by sponsor and investigator.

Upon completion of the DLT evaluation in patients in the high-dose level cohorts and confirmation that the dose is safe, patients in the low-dose level cohorts may be adjusted to the high-dose level study treatment that has completed the evaluation, with the consent of the principal investigator and the sponsor.

Subjects in the dose expansion study may be allowed to transfer to a higher dose level if the benefits outweigh the risks, as assessed by the investigator, and determined by the SMC. The higher dose level should be safe and confirmed by the phase Ia dose escalation study, as assessed by the investigator and determined by the SMC.

4.7.3 Temporary Withdrawal

Study treatment may be suspended (not more than 28 days) for any of the following treatment-related adverse events: Grade 2 or higher adverse events, if clinically indicated, study treatment should be suspended until the event returns to grade 1 or baseline levels (see Table 9)

The study drug may be discontinued for no more than 28 days until toxicity is relieved, or based on the investigator's judgment. If > 28 days, the patient continues to benefit from the treatment as assessed by the investigator, the patient may continue to receive the study treatment.

5 Study Population

5.1 Number of Subjects

- Part A: approxiamately 27 patients
- Part B: approxiamately 12 patients in no more than 2 dose levels
- Part C: approxiamatetly 60 patients in no more than 2 dose cohorts, with 30 patients at the most in one dose cohort

5.2 Inclusion Criteria

1. Patients must understand and voluntarily sign the Informed Consent Form (ICF).
2. Patients $\geqslant$ 18 years.
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 is eligible (See Appendix 6).
4. Documented positive oestrogen receptor status of primary or metastatic tumour tissue, according to the local laboratory parameters. HER-2 negative. 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) and progesterone receptor (PgR) testing in breast cancer (Allison et al., 2020).
5. Menopausal women according to one of the following criteria:
    - Prior bilateral ovariectomy;
    - Patients $\geqslant$ 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: Previous therapy failed or intolerable, or standard therapy not available.

   Part B/C: 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. Patients who are HIV positive with CD4+ T-cell counts $\geqslant$ 350 cells/uL may be eligible.

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

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

10. Life expectancy $\geqslant$ 12 weeks.

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

    - Blood routine: Absolute neutrophil count (ANC) $\geqslant$ 1.5×10^9/L; Platelet count (PLT) $\geqslant 100\times10^9$/L; Hemoglobin (HGB) $\geqslant$ 90 g/L;
    - Liver function: Serum Total bilirubin (TBIL) $\leqslant$ 1.5 Upper limit of normal value (ULN); Alanine aminotransferase (ALT) and Aspartate transferase (AST) $\leqslant$ 3×ULN in subjects without liver metastasis; ALT or AST$\leqslant$ 5×ULN with liver metastasis;
    - Renal function: Serum creatinine $\leqslant$ 1.5×ULN or estimated creatinine clearance (CLcr) $\geqslant$ 60 mL/min as calculated using Cockcroft-Gault formula;
    - Coagulation function: Activated Partial thromboplastin Time (APTT) and international normalized ratio (INR) $\leqslant$ 1.5×ULN (or within target range if on anticoagulation therapy);
    - Cardiac function: Echocardiography (ECHO) shows left ventricular ejection fraction (LVEF) > 50%.

12. 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).

5.3 Exclusion Criteria

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. Or receive mitomycin and nitrosourea within 6 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 $\leqslant$ 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. Subjects with unstable or symptomatic or progressive Central nervous system (CNS) metastasis. Subjects with a history of brain metastases who were clinically stable and who underwent Magnetic resonance imaging (MRI) or Computed tomography (CT) Subjects with CT (if not suitable for MRI) who confirm no CNS disease progression 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. History of human immunodeficiency virus HIV infection, or active bacterial or fungal infection requiring systemic treatment within 14 days prior to the first study drug treatment.

10. Presence of active syphilis infection.

11. Subjects with known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection with abnormal liver function (Absence of infection was defined as HBsAg negative, HBV DNA negative and HCV antibody negative), except to:

    - Subjects who test positive for HBsAg or HBsAb during the screening period may be enrolled if the PCR test result for HCV-RNA is < 500 IU/ml (2000 copies/mL), but receive antiviral treatment according to the investigator's assessment and undergo PCR for HBV-DNA during the study treatment period;

    - Subject has a positive test for HCV antibody at screening and can be enrolled if the PCR test result for HCV-RNA is negative.

12. 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.

13. History of serious allergic reactions to the study drugs or excipients used in the protocol.

14. Women who are pregnant or lactating.

15. Prior use of an oral selective estrogen receptor degrader (SERD).

16. Subjects who use drugs or herbal supplements known to be moderate/strong inhibitors of CYP3A2 weeks prior to the first study drug treatment. Subjects who use drugs or herbal supplements known to be moderate/strong inducers of CYP3A4 weeks prior to the first study drug treatment.

17. Received medications which inhibits the production of stomoch acid within 2 weeks or 5 drug half-lives (whichever is longer) prior to the first dose of study drugs.

18. Received medications which inhibits P-gp within 2 weeks or 5 drug half-lives (whichever is longer) prior to the first dose of study drugs.

19. Patients with active or chronic corneal disease, other active eye disease requiring ongoing treatment, or any clinically significant corneal disease for which drug-induced keratopathy cannot be adequately monitored.

20. Other conditions that the investigator considers inappropriately for this study.

5.4 Subjects Withdrawal Criteria

During the study, the subject may withdrawal due to the following reasons.

5.4.1 Investigator's Decision

1. The investigator considers it necessary to stop the trial due to medical ethics;

2. Unacceptable adverse event (AE) occurred and the investigator judged that it was not appropriate for the best interest of the subjects to continue the study treatment;

3. Subjects significantly violate the study protocol, and the investigator determines that the study treatment needs to be terminated;

4. Disease progression is confirmed according to efficacy evaluation criteria (unless the investigator determines that the subject would clinically benefit from continued treatment);

5. Prior to the last biological samples, subjects use other medications that might influence the evaluation of the study drug;

6. Other conditions that the investigator determines requiring withdrawal from the study treatment.

5.4.2 Subjects Withdrawing on Their Own

Subjects who are not willing to continue the study have the right to withdraw from the study at any time. If subjects do not explicitly request to withdraw the study, but they are no long receive doses or assessments, these subjects are also considered to have "withdrawn" or "dropped out".

The primary reasons for discontinuation of treatment of a subject with the study drug will be clearly documented in the subject's medical record and recorded on the appropriate case report form (CRF). Once a treatment is permanently discontinued, the subject will not be allowed to be retreated. In the case of subjects lost to follow-up, the last-know-alive date as determined by the investigator should be reported and documented in the subject's medical records.

If a subject discontinues study drug temporarily, for example, as a result of an AE or serious adverse event (SAE), every attempt should be made to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study and the circumstances clearly noted in the source documents. The reasons for withdrawal or lost to follow-up must be documented in the CRF. All data should be collected up until the point of withdrawal included in the study. This data will be documented on CRF and included in the analysis of the study.

5.5 Criteria for Trial Termination

5.5.1 Serious Safety Concerns

1. the dose stopping criteria (see 4.4 Dose Escalation/Stopping Criteria) has been reached, in the judgement of the investigator, the trial should be stopped;

2. During the trial, a significant mistake of the trial protocol is identified, which makes it difficult to evaluate the effect of study drug, or cause significant safety concerns;

3. A significant deviation of study protocol occurs, and the investigator decide that it is difficult to evaluate the study drug with further continuation.

5.5.2 Investigator's Request

During the trial, there may be some circumstances that the investigator cannot continue a trial. It is required that the investigator must notify subjects, sponsors, and IRB or the early termination and state reasons.

5.5.3 Sponsor's Request

Sponsor may request to early terminate the trial due to following reasons:

- Financial difficulties;
- Management;
- Investigator cannot obey the protocol, and all other required laws and rules;
- The study site cannot enrol enough subjects;
- Other concerns.

If deciding to early terminate the trial, the sponsor must notify the investigator, and IRB in writing with reasons, prior to the early termination.

5.5.4 IRB and/or FDA's Request

IRB and FDA has the right to early terminate the trial.

6 Description of Study Treatment

6.1 Study Treatment

FWD1802 is an oral solid dosage form manufactured in strengths of 5mg, 25mg and 150 mg, containing the following inactive ingredients: mannitol 160C, microcrystalline cellulose PH-101, hydroxypropyl methylcellulose (LV) E5 LV, sodium starch glycolate DST, magnesium stearate LIGAMED MF-2-V-MB, silicon dioxide SYLOID 244 FP, Film Coating System Opadry®321A620006-CN Yellow, and purified water.

6.2 Administration

FWD1802 will be orally administered under fed conditions. The dose will depend on the cohort the subject is assigned to.

6.3 Study Drug Packaging and Labeling

FWD1802 tablets are packaged in the HDPE (high density polyethylene) bottles for oral solid dosage form and sealed with polypropylene (PP)/low density polyethylene (LDPE) child-resistant caps (CRC) including desiccant . 5 mg tablets are available in 30 mL HDPE bottles/CRC of 30 film coated tablets, 25 mg and 150 mg tablets are available in 60 mL HDPE bottles/ CRC of 35 film coated tablets. The contents of the label will be in accordance with all applicable regulatory requirements. An example of a study drug label for FWD1802 is shown in

IND Study No.: XX
Protocol Number: FWD1802-001

FWD1802 Tablet 5 mg, 25 mg, 150 mg
For oral use, Administer as per protocol

Lot No.: XXXX Expiry Date: XXXX Subject Number: XXXX

Dosage Units: XX tablets per bottle Storage condition: Stored at ≤25℃, sealed and dried, protected from light.

For Clinical Trial Use Only

Study Sponsor: Shenzhen Forward Pharmaceuticals Co., Ltd.

Caution: New drug limited by United States law to investigational use

Figure 2.

IND Study No.: XX Protocol Number: FWD1802-001

FWD1802 Tablet 5 mg, 25 mg, 150 mg
For oral use, Administer as per protocol

Lot No.: XXXX Expiry Date: XXXX Subject Number: XXXX

Dosage Units: XX tablets per bottle	Storage condition: Stored at ≤25℃, sealed and dried, protected from light.
For Clinical Trial Use Only	
Study Sponsor: Shenzhen Forward Pharmaceuticals Co., Ltd.	
Caution: New drug limited by United States law to investigational use	

Figure 2. An example of FWD1802 label

6.4 Study Drug Storage

The study drug should be stored in sealed and dry containers, 2~8℃, keep out of light, as per the requirements on the label.

Study drugs must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive the study drugs. Only authorized site staff may supply or administer the study drugs. All study drugs must be stored in a secure area with access limited to the investigator and authorized site staff. Investigational sites should use appropriate labeling, which addresses storage conditions and expiration post dispensing, per institutional and regulatory guidelines. Shenzhen Forward Pharmaceuticals Co. Lt will assure that the stability of the study drug is monitored to ensure suitability for continued use at the investigational site.

The details information of study drug please refer to 3.2 P Drug Product.

6.5 Study Drug Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and maintaining dispensing records. Any study drug that is not used must be recorded in the source and/or dispensing records. Missed doses should be clearly documented along with the reason. All study drug supplies and associated documentation will be reviewed and verified by the study monitor. Study drug should be retained by the site; the site will follow the pharmacy instructions on disposal and/or destruction of all unused supplies. Copies of all forms, and documentation regarding drug receipt and drug accountability records, will be retained according to the regulations governing record retention.

6.6 Study Drug Handling and Disposal

When preparing FWD1802 appropriate precautions for handling chemicals should be taken by the investigational staff, according to institutional policy, although no special precautions need to be taken. After completion of the study, all unused FWD1802 will be inventoried and packaged for shipment by the site to a designated destruction facility or

will be destroyed locally at the investigational site. The study monitor will instruct the site in the disposal and/or destruction of all unused FWD1802 supplies.

6.7 Concomitant Medications

Concomitant Medications means any drug other than the study drug used during the study period (including the screening period and all study visits).

If the use of the combination medications is due to an adverse event, it must be documented and reported in accordance with the relevant regulations and the adverse events and serious adverse events requirements of Section 9 of this protocol.

The supervisor must be notified if the use of the combination medications affects the subject's participation in the study.

Details of all drug combinations must be recorded, including drug name, reason for use, start date, end date or continuation date, indication, and dosage.

The use of other antitumor treatments or experimental drugs is prohibited during the study period. Palliative radiotherapy and bisphosphonate therapy for bone lesions are permitted. Herbal preparations or related over-the-counter preparations containing herbal ingredients are prohibited during the study and treatment period (For details please see Appendix 5).

6.8 Assessment of Compliance

When subjects are dosed at the study site, they will receive study drugs directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug will be confirmed prior to dosing by a member of study site staff other than the person administering the study drug. Study site personnel will examine each subject’s mouth to ensure that the study drug was swallowed.

7 Study Procedures

The study procedures to be conducted for each subject enrolled in the study are described in the text that follows and presented in Table 1, Table 2 and Table 3. The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization.

7.1 Subject Identification

Subjects appropriate for this trial will be identified by the investigator (or designee) who will make a preliminary determination of the subject's eligibility for the trial in accordance with the provisions of the study protocol.

Documentation of the personally signed and dated Informed Consent Form (ICF) for each subject is required before initiating the screening process. After written ICF has been obtained and eligibility to participate established, investigative site personnel will obtain the subject's identification number and study drug assignment as appropriate.

7.2 Study Start and End of Study Definitions

The start of the study is defined as the date the first subject, who is subsequently enrolled, signs an ICF. The point of enrolment occurs at the time of subject number allocation. The end of study is defined as the date of the last subject's last assessment.

7.3 Description of Assessments

7.3.1 Laboratory Assessments

All protocol required clinical laboratory assessments should be performed at the investigational site's local laboratory. All clinical laboratory results must be documented on the CRF and reference ranges and safety parameters must be provided for each laboratory used. The following assessments will be performed and evaluated during the study.

Table 10 Laboratory Assessments

Hematology	red blood cell counts (RBC), white blood cell counts (WBC), and differential counts (neutrophils (NE), lymphocytes (LY#), monocytes (MO#), eosinophils (EO#), and basophils (BA)), platelet count (PLT), hemoglobin (HGB), and hematocrit (HCT)
Coagulation Function	PT (Prothrombin Time), APTT (Partial Thromboplastin Time), INR (International Normalized Ratio), Thrombin time (TT) and fibrinogen (FIB)
Fasting Serum Biochemistry	ALT, AST (Aspartate Transaminase), GGT (Gamma-glutamyl Transpeptidase), TBIL (total bilirubin), DBIL (direct bilirubin), BUN (Urea Nitrogen) or urea, Cr (Creatinine), UA (uric acid), GLU (blood glucose), potassium, sodium, chlorine, calcium, phosphate, magnesium, TP (total protein), ALB (albumin), albumin/globulin ratio, LDH (Lactate Dehydrogenase), TBA (Total Bile Acid), TG (Triglyceride), CK (Creatine kinase), CK-MB (creatine kinase isoenzyme)and ALP (Alkaline Phosphatase).

Pregnancy Test	serum β-Human Chorionic Gonadotropin (β-HCG). Lack of childbearing potential must be noted in the source documents, if applicable.
Urinalysis	specific gravity, pH, white blood cells, red blood cells, α1 microglobulin, β macroglobulin, occult blood, proteins and glucose.
Infectious Disease Screening	HCV, HBV, HIV, syphilis, etc., but if the subject can present the test results done within 4 weeks prior to the administration, the screening can be exempted.

7.3.2 Medical History

Medical history, including details of illnesses and allergies, date(s) of onset, whether condition(s) is currently ongoing, and medication history (anti-tumor therapies), including nicotine and alcohol use, will be collected for all subjects during screening.

7.3.3 Physical Examination

A complete physical examination should include source documentation of general appearance, and following body 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.

Height, and body weight will be collected at specified time points.

7.3.4 Vital Signs

Vital signs measurement includes respiratory rate, heart rate, body temperature and blood pressure. Heart rate and blood pressure will be first checked in the seat position and then in the standing position at every time point of the scheduled plan.

7.3.5 Electrocardiogram

Standard 12-lead ECG assessments will be performed, after resting in supine position for at least 5 min to assess heart rate, rhythm, and interval information such as PR, QRS, QT, QTc and so on. The Investigator will review the ECGs for any clinically significant abnormalities to ensure subject safety.

If a subject has possible cardiac-related symptoms, repeat ECGs will be obtained every 30 min±3 min until the waveform reverts to its baseline appearance, or symptoms resolve, or are determined not to be cardiac-related. Participants with cardiac-related symptoms that are associated with ECG changes will be transferred to appropriate emergency department for further evaluation and treatment at the discretion of the Investigator.

7.3.6 Echocardiogram

Echocardiogram will be performed during the study and left ventricular ejection fraction (LVEF) was recorded.

7.3.7 ^{18}F-FES PET/CT

The patients underwent both 18F-FES and ^{18}F-FDG PET/CT at screening period and C2D8 to monitor the detect in ER target occupation and inhibition. The detection iterval between 18F-FES and ^{18}F-FDG PET/CT was within 7 days.

All of the patients were requested to fast for more than 4 h prior to ^{18}F-FES PET/CT scans to eliminate the excretion of ^{18}F-FES from the hepatobiliary system and the gastrointestinal tract, which might interfere with image interpretation in the pelvic cavity.

7.4 Study Procedures

After signing the informed consent form, the subjects will complete the screening and baseline assessment during the screening period and be enrolled in the study after confirming that they meet the inclusion criteria.The investigator selects subjects who will understand the study and comply with the instructions. At each visit, the investigator shall remind subjects to follow the study protocol procedures. If the subjects withdraw from the study or terminate the treatment for any reason, they should return to the hospital for EOT visit and follow-up visits during the follow-up period. Blood samples should be collected after discontinuing the drugs and safety-related follow-up should be conducted (SFU visit).

7.4.1 Screening Period (Day -28~Day -1) for All Subjects

After signing the ICF, a subject should undergo medical screening to assess whether he/she is eligible to participate in the study according to the inclusion criteria. The screening evaluation will be completed within 28 days prior to the first administration of the investigational drug.

Administrative Procedures:

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Medical history
- Concurrent diseases

Clinical Procedures/Assessments:

- Weight
- Body height
- Physical examination
- vital signs

- ECOG Score
- 12-lead ECG
- Echocardiogram

Laboratory tests:

- Blood Chemistry
- Hematology
- Coagulation
- Urinalysis
- Virology: HBV, HCV, and HIV
- Pregnancy
- COVID-19

Efficacy Assessments:

- Tumor Assessmen

Biomarker Exploration:

- ^{18}F-FES PET/CT15

Other:

- Adverse events and concomitant medication;

The information above should be obtained from the source file. For test values outside the normal range (outliers), the investigator will assess whether to repeat the test.

The investigator will review patient's medical history at the time of screening period. The history includes all current active diseases and any other conditions deemed clinically significant by the investigator. The date of last prior anticancer therapy(s) and treatment response must be recorded. Pre-enrollment imaging data can be collected for the investigator's reference. A complete medication history within 28 days prior to the first administration of the study drug should be reported.

7.4.2 Treatment Period

7.4.2.1 Part A study

See Table 1 for details.

7.4.2.2 Part B study

See Table 2 for details.

7.4.2.3 Part C study

See Table 3 for details.

7.4.3 Post Treatment Follow-up Visit

7.4.3.1 End of treatment (EOT) visit

The end-of-treatment (EOT) will occur at the earliest day possible within 7 days after the last dose of FWD1802 or the subject decides to withdraw from study treatment for any reason.

Clinical Procedures/Assessments**:**

- Weight
- Body height
- Physical examination
- vital signs
- ECOG Score
- 12-lead ECG
- Echocardiogram;

Laboratory tests**:**

- Blood Chemistry
- Hematology
- Coagulation
- Urinalysis

Other:

- Adverse events and concomitant medication;

7.4.3.2 Safety follow-up (SFU)

Mandatory safety follow-up (SFU) should be performed at 28 ±7 days after the last administration and prior to the initiation of a new anti-tumor therapy. Subjects who

discontinue the study due to an unacceptable adverse event should be followed until AE relieves to grade 0-1 or AE is stable. If EOT visit is within the safety follow-up window, no further safety follow-up is required.

Adverse events and concomitant medication;

7.4.3.3 Long term follow-up (LTFU)

LTFU is survival follow up. After completion of the treatment and safety follow-up period, all the subjects will be followed for survival status. Subjects will be contacted by phone or in person every 12 weeks ±7 days after discontinuation to assess survival status until subject death or study termination. Survival and subsequent antitumor therapy will be collected during these calls/interviews.

7.5 Biological Samples

7.5.1 PK Samples

Blood samples will be collected from all the subjects for PK analysis.

- **Part A study:**

Table 11 PK Sample Time Points and Time Windows

Time for Blood Collection	**Single Dosing Study**			**Multiple Dosing Study**				
	Cycle 0 (4 Days)			Cycle 1 (28 Days)			Cycle 2 (28 days)	⩾Cycle 3 (28 days)
	D1	D2	D3	D1	D8	D15	D1	D1
-1h (prior to dosing)	X			X	X	X	X	X
0.5 h	X					X		
1 h	X					X		
2 h	X					X		
3 h	X					X		
4 h	X					X	X	X (±2h)
6 h	X					X		
8 h	X					X		
10 h	X					X		
24 h	X	X	X			X (C1D16 pre-dose)		

- **Part B study:**

Time for Blood Collection	**Multiple Dosing Study**				
	Cycle 1 (28 Days)			Cycle 2 (28 days)	⩾Cycle 3 (28 days)
	C1D1	C1D8	C1D15	C2D1	C3D1
-1h (prior to dosing)	X	X	X	X	X
0.5 h	X		X		

1 h	X		X		
2 h	X		X	X	
3 h	X		X	X	
4 h	X		X	X	
6 h	X		X	X	
8 h	X		X		
10 h	X		X		
24 h	X（C1D2 pre-dose）		X（C1D16 pre-dose）		

- **Part C study：**

Time for Blood Collection	**Multiple Dosing Study**		
	Cycle 1 (28 Days)	Cycle 2 (28 days)	≥Cycle 3 (28 days)
	C1D1	C2D1	C3D1
-1h (prior to dosing)	X	X	X
0.5 h			
1 h			
2 h	X	X	
3 h	X	X	
4 h	X	X	X (±2h)
6 h	X	X	
8 h	X	X	
10 h	X	X	
24 h	X（C1D2 pre-dose）	X（C2D2 pre-dose）	

Table 12 PK Samples Time Windows

Collection Time Point	**Time window**
D1 (prior to dosing)	Within 60 min
0~4 h after administration (4 h included)	±3 min
4~10 h after administration (10 h included)	±5 min
10~24 h after administration (24 h included)	±10 min
Greater than 24 after administration (24 h not included)	±30 min

7.5.2 Sample Preparation

Details of sample collection, processing, shipping and storage will be described in the separately Laboratory Manual.

Samples will be analyzed using a previously validated method, which will be described in the Laboratory Manual of the study site.

8 Lifestyle and/or Dietary Management

8.1 Pregnancy Precautions

8.1.1 Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty until becoming post-menopausal, unless permanently sterile or ovarian failure with medical documentations.

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

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

A male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

8.1.2 Contraception Requirements for Female Subjects of Childbearing Potential

Complete abstinence from intercourse of reproductive potential is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Sexually active female subjects of childbearing potential must agree to use at least 1 highly effective contraception and 1 additional method at least 1 month prior to initiation of the study, during the study, and for 6 months after the last administration of the study drug. Female subjects 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.

8.1.3 Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods 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 ER+/HER2- unresectable locally advanced or metastatic breast cancer with or without ESR1 mutation, which may reduce the efficacy of the contraception method.
- Intrauterine device
- Tubal sterilization

- Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

8.1.3.1 Methods that are Considered Less Highly Effective

- 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 methods) are also considered acceptable, but not highly effective, birth control methods.

8.1.4 Unacceptable 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.

Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated, and pregnancy testing will be conducted at specified times

8.2 Meals and Dietary Restrictions

FWD1802 (and palbociclib) is administrated after meal (within 30 minutes) with approximately 240 ml water. The subjects should start the recommended meal 30 minutes before administration of the drug product. Other dietary restrictions are as follows:

- During each dosing session, subjects will abstain from ingesting caffeine or xanthine containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours prior to the start of dosing until collection of the final PK samples during each session.

- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing and during each session.

- Use of tobacco products is not allowed 3 months prior to the screening visit.

- Use of traditional Chinese medicines or herbal products is not allowed 2 weeks prior to and during the study.

8.3 Physical Activity

- Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watching television, reading).

- Subjects will be advised to stay indoors to avoid ≥ 15 min extreme exposure to the sun or sunbathing.

9 Assessments of Adverse Events

9.1 Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this clinical study protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

The following definitions of terms are guided by the International Conference on Harmonization and the US Code of Federal Regulations and are included here verbatim. The terms “serious adverse event” and “adverse event” are commonly used by the Sponsor.

9.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity (grade) of the condition.
- New conditions detected or diagnosed after investigational product administration even though may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae associated with a suspected interaction of the investigational product with a concomitant medication.

9.1.2 Serious Adverse Event Definition

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening-

  Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to any adverse drug experience (AE) that places the subject or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires in subject hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the subject or participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital abnormality/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject or participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

9.2 Relationship of Adverse Event to Study Drug

The investigator or designated physician-sub investigator responsible for the care of the subjects in the study will assess the relationship of each AE or laboratory abnormality to FWD1802 using clinical judgement and the following considerations:

- No: Evidence exists that the AE has an etiology other than the FWD1802. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- Yes: There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, blood draw) should be assessed using the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study procedure.

- Yes: There is reasonable possibility that the adverse event occurred as a result of protocol procedures.

9.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Subjects are also required to report any AEs and/SAEs, including but not limited to loose stools or diarrhea.

9.4 Recording AEs and SAEs

9.4.1 All Adverse Events Regardless of Seriousness

Any adverse medical condition or laboratory abnormality with an onset date before initial dose of study drug administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry, and any events of Grade 3 or 4 severity that occur up to 14 days before study entry (even if resolved prior to study entry) should be recorded in the appropriate section of the CRF.

All AEs occurring from initial FWD1802 administration up to 30 days following the last dose of FWD1802 must be recorded as an AE in the subject's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study drug.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the subject begins taking FWD1802 is also considered an AE.

9.4.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry and hematology) or other abnormal assessments (e.g., ECGs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions as defined in Section 9 Assessments of Adverse Events. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.4.3 Grading of Adverse Events

AE will be graded according to CTCAE v5.0.

9.5 Reporting Adverse Events

9.5.1 All AEs

All events meeting the criteria for AE that occur after the initial dose of FWD1802 during treatment, or within 30 days of the last dose of FWD1802 (including all deaths) must be reported to the Sponsor regardless of cause or assessed relationship to therapy. SAEs will be collected from the time of signed ICF, throughout the entire study, till the follow-up period. SAEs occurring at any time, even after the reporting timeline, must also be reported immediately if suspected to be associated with the study drug.

- The Investigator should instruct the subject to be truthful about changes following the administration. Inducted questions should be avoided;
- Closely monitor AEs or unexpected toxicities (including symptoms, signs, and laboratory tests), analyse reasons and follow-up;
- For AE report, include/attach detailed descriptions about symptions, severity, time, duration, measurement, the association with study drug, etc. Record should be signed and dated by the Investigator;
- All AEs should be followed-up until resolve, stable or loss of follow-up.

9.5.1.1 SAE

Unless stated by the protocol or other profiles (i.e. investigator's brochure), SAE should be reported to the Sponsor or sponsor assigned safety representative within 24 h of knowledge. The written report should include/attach detailed descriptions including copies of hospital case reports, autopsy reports (if any), and other documents when requested and applicable to the SAE Report. If these items are not immediately available, they are to be provided as soon as possible as a follow-up to the initial SAE Report. For all fatal or life-threatening SAEs contact the Sponsor immediately (as listed on title page of the protocol) and then fax or email the initial report as soon as possible.

Follow-up will be conducted by the Sponsor or sponsor assigned safety representatives and as needed with investigational site personnel to obtain any additional information needed to complete the reporting of the event.

9.5.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Unexpected adverse event or suspected adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application.

Initial reporting: IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

SUSAR must be reported to FDA as soon as possible but no later than within 15 calendar days following the sponsor's initial receipt of the information.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

Follow-up reporting: Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

9.5.2 Follow-Up of AE/SAE

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to Sponsor on the subject's condition.

AEs that are ongoing with a toxicity of Grade 3 or 4, or have a relationship to investigational drug that is suspected, will be queried for resolution at study conclusion and until resolved or stable and not clinically significant. All SAE's will be followed until they completely resolve, or are otherwise stable. Subjects who discontinue the study due to disease progression should also be followed until adverse event resolves to grade 0-1 or is stable. Once resolved/stabilized, the appropriate AE CRF page(s) or SAE form(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

As reasonably requested by the Sponsor, the investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. If a subject dies during participation in the study or during a recognized follow-up period, Sponsor will be provided with a copy of any post-mortem findings, including histopathology, if possible.

9.5.3 Post-Study Reporting Requirements

Although such information may not be routinely sought or collected by Sponsor, SAEs that occur after the subject has completed the clinical study may be reported. Such cases will be evaluated for expedited reporting.

9.5.4 Pregnancy

The risks of treatment with FWD1802 during pregnancy have not been evaluated. To ensure participant's safety, each pregnancy in a subject on drug must be reported to the sponsor within 24 h of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy and follow-up will be documented, and should include

an assessment of the possible relationship to the IND drug of any pregnancy outcome. Pregnant women who are abortive or need induction of labor should be reported as an SAE.

Pregnancy outcomes must also be collected for the female partners of any males who takes study treatment in the trial, pending consent from the mother.

10 Statistics

A Statistical Analysis Plan (SAP) will be written prior to database lock. The SAP will detail the planned statistical analysis methods to be conducted. A summary of the proposed statistical analysis plan to be conducted is provided in the following sections.

10.1 Sample Size Estimate

The sample size estimate of a total of 99 subjects in this trial is based on the enrollment of all parts of the study. This number is considered adequate to determine the safety, tolerability, PK, PD and preliminary efficacy in patients with ER+/HER2- unresectable locally advanced or metastatic breast cancer. The study is summarized below.

Table 13 Sample Size Estimate for the Study

Design	Name of Study	Number of Subjects	Groups
open-label, single arm	Part A: Dose Escalation	27 subjects	5 cohorts (1~6 subjects for each dose level)
open-label, single arm	Part B: Dose Escalation	12 patients	no more than 2 dose levels
open-lable, single arm	Part C: Dose Expansion	60 subjects in total	no more than 2 dose cohorts, with 30 patients at the most in one dose cohort

10.2 Analysis Sets

10.2.1 Full Analysis Set (FAS)

All patients who received at least 1 dose of FWD1802.

10.2.2 Safety Analysis Set (SS)

All enrolled subjects who have received the investigational product at least once and have at least 1 valid safety assessment data. They will be used for listings and summaries of safety analysi.

10.2.3 Pharmacokinetic Concentration Set (PKCS)

All enrolled subjects who have received the investigational product at least once and have at least 1 valid concentration data of FWD1802. They will be used for listings and summaries of PK concentrations.

10.2.4 Pharmacokinetic Parameter Set (PKPS)

All enrolled subjects who have received the investigational product at least once and have at least 1 valid PK parameter data of FWD1802. They will be used for listings and summaries of PK parameters.

10.2.5 Pharmacodynamics Analysis Set (PDS)

All enrolled subjects who have received the investigational product at least once and have at least 1 valid (non-baseline) PD data.

10.2.6 Efficacy Analysis Set (EAS)

All enrolled subjects who have used the investigational product and have at least one efficacy observation value.

Upon completion of the dose expansion study, an integrated dose response and exposure-response analyses for the recommended phase 2 dose (RP2D) will be determined.

10.2.7 Interim Analysis

No formal interim analysis is planned for this study. But prior to the dose-expansion part, the investigator, sponsor and medical monitor will review the safety and PK data accumulated in dose-escalation part, and make the decision.

10.3 Data Handling Conventions

Missing data can have an impact on the interpretation of the study data. In general, values for missing data will not be imputed.

Where appropriate, safety data for subjects that do not complete the study will be included in summary statistics. For example, if a subject receive study drug, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

Values for missing safety laboratory data will not be imputed; however, a missing baseline result may be replaced with a screening result, if available. If no pre-study laboratory value is available, the baseline value will be assumed to be normal for the summary of graded laboratory abnormalities.

10.4 Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods, including age, gender, race, weight, past medical and surgical history, vital signs, concomitant medications, and clinical laboratory parameters.

10.5 Safety Analysis

Incidence and severity of adverse events according to the NCI-CTCAE (V 5.0) will be summarized and displayed in number/percentage. The exposure extent to the study drug will be displayed.

10.5.1 Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), Preferred Terminology (PT), will be attached to the clinical database. See Section 9 for the definition and the severity of AE.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event (TEAE) will be defined as following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided. TEAEs will also be summarized by relationship to study drug and severity. In addition. TEAEs leading to premature discontinuation of study drug and study will be summarized and listed.

All AEs collected during the course of the study will be presented in data listing with a field for treatment-emergent event (yes/no).

10.5.2 Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum and maximum) by treatment cohorts and time along with the corresponding change from baseline values.

10.5.3 Other Safety Evaluations

The results of scheduled assessments of DLTs, pregnancy tests, physical examination, ECGs, vital signs laboratory tests will be listed for each subject and summarized by dose level and scheduled time point using appropriate descriptive and graphic statistics. The change from baseline data will also be listed.

10.5.4 Pharmacokinetic Analysis

A descriptive analysis of the plasma concentration and derived PK parameters of FWD1802 and its metabolite (if possible) will be conducted by dose level. Plasma concentration patient profiles versus time and mean concentration versus time will be displayed.

10.6 Pharmacodynamics Analysis

Pharmacodynamic analysis will be performed based on PD analysis set. Explore the relationship between exposure or dose of FWD1802 and biomarkers, safety, and clinical efficacy where possible.

10.7 C-QT Analysis

Based on the changes of PK and QT interval, an exploratory statistical analysis of C-QT will be performed.

The QT/QTc interval at each time point and its change from baseline will be analyzed descriptively, and the line chart will be used to describe the change at each time point and between each cohorts.

Baseline correction (ΔQTc) and placebo correction (ΔΔQTc) will be applied to the obtained QT/QTc interval, and ΔQTc will be used as the dependent variable to measure the degree of drug effect on QT/QTc, such as a linear mixed effects model.

If possible, combined with the changes of investigational product concentration and QT/QTc interval, model exploration analysis will be performed.

10.8 Preliminary Efficacy Analysis

- Objective Response Rate (ORR): The proportion of subjects with tumors shrinking to a certain amount or volume and maintaining a certain period, including the complete response (CR) and partial response (PR) cases. The objective response rate and 95% confidence interval will be calculated.

- Duration of response (DoR): The time from the first assessment of CR or PR to the first assessment of disease progression or death of any cause. For subjects who continue to survive without progression after meeting response criteria, the duration of response will be deleted on the last assessable tumor assessment date or the last disease progression follow-up date.

- Disease control rate (DCR): The proportion of patients with tumors shrinking or stabilizing and remaining for a certain period includes cases of CR and PR and stable disease (SD).

The ORR and its exact 95% Clopper-Pearson confidence interval will be calculated. The CBR, DCR will also be calculated similarly. All of the time-to-event data (PFS, DOR,OS) will be estimated using Kaplan-Meier method, and the median along with two-sided 95% CI will be displayed(use the Greenwood's formula for estimation of standard errors).

11 Study Conduct Considerations

11.1 Quality Check (Study Monitoring)

In accordance with applicable regulations including GCP, and rocedures, Shenzhen Forward Pharmaceuticals Co. Lt monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical and Shenzhen Forward Pharmaceuticals Co. Lt requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the source records will be identified.

Shenzhen Forward Pharmaceuticals Co. Lt will monitor the study and site activity to verify that the:

- Data are authentic, accurate and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Shenzhen Forward Pharmaceuticals Co. Lt may conduct a quality assurance audit. Regulatory agencies may also conduct regulatory inspections of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.3 Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP and Shenzhen Forward Pharmaceuticals Co. Lt procedures.

In addition, Shenzhen Forward Pharmaceuticals Co. Lt reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Shenzhen Forward Pharmaceuticals Co. Lt will discuss with this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, Shenzhen Forward Pharmaceuticals Co. Lt will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, Shenzhen Forward Pharmaceuticals Co. Lt ill promptly inform the investigator or the head of the medical institution (where applicable) and the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by the applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason(s) for the suspension or premature discontinuation.

11.4 Record Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staffs. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including the ability to re-generate a hard copy, if required. Furthermore, the investigator must ensure that there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Shenzhen Forward Pharmaceuticals Co. Lt will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Shenzhen Forward Pharmaceuticals Co. Lt standards/procedures; otherwise, the retention period will default to 5 years.

The investigator must notify Shenzhen Forward Pharmaceuticals Co. Lt of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator leaves the site.

11.5 Provision of Study Results and Information to Investigator

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, Shenzhen Forward Pharmaceuticals Co. Lt will provide the investigator with a full summary of the study results. In addition, the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at any Shenzhen Forward Pharmaceuticals Co. Lt's site or other mutually agreeable location.

11.6 Data Management

Shenzhen Forward Pharmaceuticals Co. Lt's or an appointed third party's data management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets which support the protocol objectives. Subject data will be entered into Shenzhen Forward Pharmaceuticals Co. Lt released CRFs and combined with data provided from other sources (e.g., diary data, laboratory data) in a validated data system. Clinical data management will be performed in accordance with the applicable Shenzhen Forward Pharmaceuticals Co. Lt's or third party's standards and will include data cleaning procedures with the objective of removing errors and inconsistencies in the data which could otherwise impact on the analysis and reporting objectives, or the

credibility of the clinical study report. Adverse events and concomitant medications terms will be coded using the standards of MedDRA. Original CRFs will be retained by Shenzhen Forward Pharmaceuticals Co. Lt, while the investigator will retain a copy. In all cases, subject initials will not be collected nor transmitted to Shenzhen Forward Pharmaceuticals Co. Lt.

12 Ethics

12.1 Regulatory and Ethical Considerations

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- International Conference on Harmonization E6 Good Clinical Practice (GCP) Consolidated Guideline.

- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws and regulations.

12.2 Ethics Review

Prior to initiation of the study, the investigator must provide the sponsor with a copy of the written institutional review board (IRB) approval of the protocol and study participant information and consent form (PICF). This approval letter will identify the study informed consent form (ICF) by date and the study protocol by protocol number, title and date. The investigators will receive all the documentation needed for submitting the current protocol to the IRB. The composition of the IRB will also be provided to the sponsor. If approval is suspended or terminated by the IRB, the investigator will notify the sponsor immediately.

It is the responsibility of the investigator to report study progress to the IRB as required or at intervals not greater than one year.

The principal investigator at each study site or his/her nominee, will be responsible for reporting any SAEs to the IRB as soon as possible, and in accordance with the guidelines of the IRB.

A copy of the approval letter from the IRB must be received by Shenzhen Forward Pharmaceuticals Co. Lt prior to shipment of drug supplies to the investigator. The approval letter must contain, at a minimum, the protocol title and/or number, the investigator's name, and the date of approval.

Changes to the protocol and ICF must also be submitted to the IRB for review and approval. Any new or revised IRB approval letters must be forwarded to Shenzhen Forward Pharmaceuticals Co. Lt promptly. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended PICF before obtaining any new subjects' consent to participate in the study. Records of the IRB annual review, and if applicable, approval of all documents pertaining to this study must be sent to Shenzhen Forward Pharmaceuticals Co. Lt and kept on file with the investigator. These documents are subject to regulatory authority or Shenzhen Forward Pharmaceuticals Co. Lt inspection at any time during the study and for 2 years following the last marketing application for the drug. The Sponsor will be responsible for reporting all serious, life threatening or fatal AEs with a causal relationship to the investigational product to appropriate regulatory agencies within their required time lines.

12.3 Written Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this phase 1/2 clinical trial after adequate explanation of the aims, methods, objectives, and potential hazards (including insurance and other procedures for compensation in case of injury) of the study and prior to undertaking any study-related procedures. All prospective subjects will be given a copy of the approved (in writing) study ICF to read.

The investigator must utilize an IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent. Source documentation of the informed consent process must indicate whether informed consent was obtained prior to participation in the study.

It will be pointed out that subjects can refuse to participate in the study, or withdraw from the study without prejudice to further care and treatment. Ample time and opportunity will be allowed for each subject to enquire about details of the study and to decide whether or not to participate in the study.

Subjects will be informed of any significant new finding, which arises during the course of the research that may affect their decision to continue participation.

12.4 Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code will be recorded on any form or biological sample submitted to the sponsor, IRB or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Sponsor, including but not limited to the investigator brochure, this protocol, eCRF, the study drug, and any other study information, remain the sole and exclusive property of Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13 Data recordkeeping

13.1 Inspection of Records

The investigator should understand that all records including source documents for this clinical trial should be made available to appropriately qualified personnel from Sponsor or its representatives, or to regulatory authority or health authority inspectors.

13.2 Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data).

All source documents, CRFs and study documentation will be kept by the investigator for the appropriate retention period as stipulated by local regulations and ICH-GCP.

No trial document should be destroyed without prior written agreement between the sponsor and the investigator. Study data is always moved to an offsite location after study conduct is complete, the investigator must notify the sponsor in writing of the new responsible person and/or the new location.

14 Financing and Insurance

Subjects may be compensated for the time that they spend participating in the study using a formula determined by the study site.

Insurance will be provided in conformity with the ICH-GCP for all subjects involved in the study. The subject should not take part in any other clinical study whilst enrolled in this study. The subject should report any health injury that could have occurred as a result of the clinical study to the investigator without delay.

15 Publishing

Following completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Data is the property of the Sponsor and cannot be published without prior authorization granted by the Sponsor, but data and publication thereof will not be unduly withheld.

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Appendix 1

Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)

1. Introduction

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines (Eisenhauer et al., 2009) for the study with regards to investigator assessment of tumor burden including protocol-specific requirements for this study.

2. Measurability of tumor at baseline

2.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorised measurable or non-measurable as follows:

2.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on ‘Baseline documentation of target and non-target lesions’ for information on lymph node measurement.

2.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- • Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- • Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- • Blastic bone lesions are non-measurable.

Cystic lesions:

- • Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- • 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- • Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

2.2 pecifications by methods of measurements

2.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

2.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above EUROPEAN JOURNAL OF CANCER 45 (2009) 228 – 247 231 the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effects of treatment (e.g., with certain taxane compounds or

angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

3. Tumor response evaluation

3.1Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

3.2. Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm · 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3.3. Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

3.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

3.3.2. Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become ‘too small to measure’. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, when non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

3.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

3.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden.

Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

3.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

3.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

3.4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 the next page provides a summary of the overall response status calculation at each time point for patients at baseline.

3.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing

argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

3.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 14 Time Point Response

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non-CR/Non PD	No	PR
CR	NE	No	PR
RR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/non PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable (relevant when no NTLs at baseline)

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

4.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

3.5. Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

3.6. Confirmatory measurement/duration of response

3.6.1. Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

3.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

3.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the

minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

3.7. Progression-free survival/proportion progression-free

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

3.8. Independent review of response and progression

For trials where objective response (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter.

3.9. Reporting best response results

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response

2. Partial response

3. Stable disease

4. Progression

5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumor assessments not repeated/incomplete; other (specify)).

Normally, all eligible patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should not be based on a selected ‘evaluable’ subset.

Appendix 2

ECOG Performance Status*(Oken et al., 1982)

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

Appendix 3

A formula(Cockcroft DW, 1976) has been developed to predict creatinine clearance (Ccr) from serum creatinine (Scr) in adult males:

$$C_{cr} = \frac{(140 - age)(wt\ kg)}{72 \times S_{cr}(mg/100\ ml)}$$

(15% less in females).

Appendix 4

SOP for Emergency

- Special treatment

1. Stop administration;
2. Monitoring vital signs: ECG, blood pressure, respiration, temperature;
3. Gastric lavage: 1%~2% sodium chloride solution or 1:5000 potassium permanganate solution;
4. Catharsis: Sodium sulfate 15~30 g, add water 200 mL;
5. Enema: Wash with 1% lukewarm soapy water (about 5000 mL) at high level continuously.

- **Supportive therapy**

1. Sedation and oxygen administration;
2. Establish intravenous infusion channels, open respiratory channels, and give endotracheal intubation, cardiac massage and ventilator assisted breathing support when necessary;
3. Adequate fluid replacement to maintain circulating blood volume: intravenous injection of normal saline or glucose sodium chloride, according to the condition of colloid supplement to ensure circulation osmotic pressure;
4. Strengthen the heart, improve the pressure, maintain the stability of blood pressure, and ensure the blood supply of important organs: 20-60mg adrenal corticosteroid plus 5% glucose 50-250ml intravenous infusion can be given first, and dopamine can be pumped for maintenance after the blood pressure is stabilized;
5. Diuretic, diuretic drugs such as furosemide were given according to the volume of urine, sodium bicarbonate was given in appropriate amount, and the urine was alkalized;
6. Maintain the balance of water, electrolyte, acid and base;
7. Anti-arrhythmia;
8. Symptomatic treatment to maintain nitrogen balance.

- **Anti-allergy treatment**

1. Promethamine 10 mg or promethazine 25-50mg, supine, oxygen inhalation, ensure the airway patently;

2. 0.1% epinephrine 0.1-0.2ml plus 5% glucose by intravenous drip;

3. Use glucocorticoids such as dexamethasone;

- **Correct respiratory and circulatory failure**

Give oxygen or artificial respiration, with kelamine 0.375 g, lobelin 3~6mg injection alternately, every 15~30 minutes. If necessary, intravenous injection 1~2 times strong heart glycoside drug digitalis preparation.

Appendix 5

CYP3A and P-gp Inducers and Inhibitors

	Strong Inhibitors	**Strong Inducers**
CYP3A4	cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir (and/or dasabuvir), posaconazolee, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, ceritinib, clarithromycin, idelalisib, nefazodone, nelfinavir	apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin
	Moderate Inhibitors	**Moderate Inducers**
	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, isavuconazole, tofisopam, verapamil	bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib
P-gp	**Strong/Moderate Inhibitors**	**Strong/Moderate Inducers**
	amiodarone, clarithromycin, cobicistat, cyclosporine, dronedarone, erythromycin, itraconazole, ketoconazole, lapatinib, lopinavir and ritonavir, quinidine, ranolazine, saquinavir and ritonavir, verapamil	--
Reference:https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers		

Proton pump inhibitors (PPIs)

PPIs	lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), rabeprazole (AcipHex), and esomeprazole (Nexium)
Reference: https://www.fda.gov/media/144026/download	

Appendix 6

ESR1 Mutations in Breast Cancer

Nuclear receptor location	Mutation
AF1	S47T
	A65V
	N69K
	P147Q
	G160D
DBD	P222S
	R233G
Hinge	K252N
	R271K
	E279V
	S282C
	A293V
	K303R
	S329Y
	G344D
AF2/LBD	L370F
	E380Q
	V392I
	M396V
	N407I
	V418E
	G420D
	M421V
	S432L
	M437I
	G442R
	F461V
	S463P
	L466Q
	E471D
	V478L
	R503W
	E523Q
	H524L
	K531E
	N532K
	V533M
	V534E
	P535H/T
	L536H/Q/P/R
	Y537C/D/H/N/S
	D538G/N
	L540Q
	E542G
	A546D/T
	L549P

	R555C/H
	G557R
	T570I
	S576L
	A593D

Note: Location of ESR1 missense mutations found in clinical samples. 47/62 identified mutations occur in the LBD, and several are associated with ligand-independent activation of ER. AF1, activation function 1; DBD, DNA binding domain; AF2, activation function 2; LBD, ligand binding domain(Dustin, Gu, & Fuqua, 2019).