Official Title:	A PHASE 1/2 OPEN LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF ZN-c5 ALONE AND IN COMBINATION WITH PALBOCICLIB IN SUBJECTS WITH ESTROGEN-RECEPTOR POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 NEGATIVE ADVANCED BREAST CANCER
NCT Number:	NCT03560531
Document Date:	20-Apr-2021

A PHASE 1/2 OPEN LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND ANTI-TUMOR ACTIVITY OF ZN-c5 ALONE AND IN COMBINATION WITH PALBOCICLIB IN SUBJECTS WITH ESTROGEN-RECEPTOR POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2 NEGATIVE ADVANCED BREAST CANCER

Protocol Number: ZN-c5-001

EUDRACT Number: 2018-001364-27

IND Sponsor: Zeno Alpha, Inc.

Protocol Version: 6.0

20 April 2021

Table of Contents

STATEMENT OF COMPLIANCE 6
1 PROTOCOL SUMMARY 7
1.1 Synopsis 7
1.2 Schema 11
1.3 Schedule of Activities 12
2 INTRODUCTION 16
2.1 Study Rationale 16
2.2 Background 18
2.3 Risk/Benefit Assessment 19
2.3.1 Known Potential Risks 19
2.3.2 Known Potential Benefits 20
2.3.3 Assessment of Potential Risks and Benefits 20
3 OBJECTIVES AND ENDPOINTS 21
4 STUDY DESIGN 24
4.1 Overall Design 24
4.2 Scientific Rationale for Study Design 24
4.3 Justification for Dose 24
4.4 End of Study Definition 24
5 STUDY POPULATION 26
5.1 Inclusion Criteria 26
5.2 Exclusion Criteria 27
5.3 Lifestyle Considerations 28
5.4 Screen Failures 28
5.5 Strategies for Recruitment and Retention 29
6 STUDY INTERVENTION 30
6.1 Study Intervention(s) Administration 30
6.1.1 Study Intervention Description 30
6.1.2 Dosing and Administration 30
6.1.3 Definition Of MTD and RP2D 31
6.1.4 Monotherapy Dose Escalation 31
6.1.5 Combination Dose Escalation 32
6.1.6 Monotherapy Expansion 32
6.1.7 Monotherapy Phase 2 33
6.1.8 Combination Phase 2 33
6.2 Preparation/Handling/Storage/Accountability 34
6.2.1 Acquisition and Accountability 34
6.2.2 Formulation, Appearance, Packaging, and Labeling 34
6.2.3 Product Storage and Stability 35
6.2.4 Preparation 35
6.3 Measures to Minimize Bias: Randomization and Blinding 35
6.4 Study Intervention Compliance 35
6.5 Concomitant Therapy 35
6.5.1 Prophylactic medications and therapy 35
6.5.2 Use of CYP3A4 and CYP2C9 inhibitors and inducers 36
6.5.3 Use of other inhibitors or inducers 36
6.5.4 Additional prohibited medications 36

6.5.5 Rescue Medicine 36
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 37
7.1 Discontinuation of Study Intervention 37
7.2 Participant Discontinuation/Withdrawal from TREATMENT AND FROM the Study 37
7.3 Lost to Follow-Up 38
7.4 End of Treatment Visit 38
7.5 Safety Follow-up Visit 38
7.6 Disease Assessment Follow-up Visits 39
7.7 Survival Follow-up Visits 39
8 STUDY ASSESSMENTS AND PROCEDURES 40
8.1 Efficacy Assessments 40
8.1.1 Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) 40
8.2 Safety and Other Assessments 40
8.2.1 Safety Assessments 40
8.2.2 Pharmacokinetic, Pharmacodynamic, & Correlative Samples 42
8.3 Adverse Events and Serious Adverse Events 47
8.3.1 Definition of Adverse Events (AE) 47
8.3.2 Definition of Serious Adverse Events (SAE) 47
8.3.3 Classification of an Adverse Event 48
8.3.4 Time Period and Frequency for Event Assessment and Follow-Up 49
8.3.5 Adverse Event Reporting 50
8.3.6 Serious Adverse Event Reporting 50
8.3.7 Reporting Events to Participants 50
8.3.8 Special Situations Reports 51
8.3.9 Reporting of Pregnancy 52
8.4 Dose-limiting Toxicities and Toxicity Management 52
8.4.1 Definition of Dose-Limiting Toxicity Monotherapy DOse Escalation 52
8.4.2 Definition of Dose-Limiting Toxicity – Combination Dose Escalation 53
8.4.3 Toxicity Management 53
8.5 Unanticipated Problems 55
8.5.1 Definition of Unanticipated Problems (UP) 55
8.5.2 Unanticipated Problem Reporting 55
8.5.3 Reporting Unanticipated Problems to Participants 56
9 STATISTICAL CONSIDERATIONS 57
9.1 Statistical Hypotheses 57
9.2 Sample Size Determination 57
9.2.1 Monotherapy Dose Escalation and Combination Dose Escalation 57
9.2.2 Monotherapy Expansion 57
9.2.3 Monotherapy Phase 2 58
9.2.4 Combination Phase 2 58
9.3 Populations for Analyses 59
9.4 Statistical Analyses 59
9.4.1 General Approach 59
9.4.2 Analysis of the Primary Endpoint(s) 60
9.4.3 Analysis of the Secondary Endpoint(s) 60
9.4.4 Safety Analyses 60
9.4.5 Efficacy Analyses 61

9.4.6 Baseline Descriptive Statistics 63
9.4.7 Planned Interim Analyses 63
9.4.8 Sub-Group Analyses 63
9.4.9 Tabulation of Individual Participant Data 63
9.4.10 Exploratory Analyses 63
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 65
10.1 Regulatory, Ethical, and Study Oversight Considerations 65
10.1.1 Informed Consent Process 65
10.1.2 Study Discontinuation and Closure 66
10.1.3 Confidentiality and Privacy 66
10.1.4 Future Use of Stored Specimens and Data 67
10.1.5 Key Roles and Study Governance 68
10.1.6 Safety Oversight 69
10.1.7 Clinical Monitoring 69
10.1.8 Quality Assurance and Quality Control 69
10.1.9 Data Handling and Record Keeping 70
10.1.10 Protocol Deviations 72
10.1.11 Publication and Data Sharing Policy 72
10.1.12 Conflict of Interest Policy 72
10.2 Additional Considerations 72
10.3 Abbreviations 73
10.4 Appendices 76
10.4.1 List of Drugs Known to Predispose to Torsade de Pointes 76
10.4.2 Revised RECIST Guidelines (version 1.1) 77
10.4.3 ECOG Performance Status 80
10.4.4 Common Terminology Criteria for Adverse Events (CTCAE) v4.03 81
10.4.5 Contraception and Maternal/Paternal Exposure 82
10.4.6 Potential Drug-Drug Interactions 84
10.4.7 Hy's Law Definition 85
10.5 Protocol Amendment History 86
11 REFERENCES 87
12 SPONSOR SIGNATURE PAGE 88
13 INVESTIGATOR SIGNATURE PAGE 89
14 REVISION HISTORY 90

List of Tables

Table 1: Study Procedures Table 12
Table 2: Dose Escalation Rules 31
Table 3: ZN-c5 Study Dose Levels 32
Table 4: Analytes 42
Table 5: Pharmacokinetic Sampling per Study Component 43
Table 6: Full Pharmacokinetic Sampling Time Points 44
Table 7: Abbreviated ZN-c5 Pharmacokinetic Sampling Time Points 44
Table 8: ZN-c5 Dose Levels for Treatment Modification in Monotherapy Expansion and Combination Phase 2 53
Table 9: Dose Reduction Criteria ZN-c5: All Phases 55

Table 10: Time Point Response: Patients with Target (± Non-target) Disease 78
Table 11: Time Point Response: Patients with Non-target Disease Only 79
Table 12: Time Point Response: Best Overall Response 79
Table 13: ECOG Performance Status 80
Table 14: Examples of CYP3A and CYP2C9 Inhibitors/Inducers 84

List of Figures

Figure 1 ZN-c5-001 Phase 1 Monotherapy Dose Escalation, Expansion and Phase 2 11
Figure 2 ZN-c5-001 Phase 1 Combination with Palbociclib Dose Escalation and Phase 2 11

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject, and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- European Clinical Trials Directive 2001/20/EC

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. In addition, all changes to the consent form will be IRB/IEC-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 1/2 Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of ZN-c5 Alone and in Combination with Palbociclib in Subjects with Estrogen-Receptor Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breast Cancer

Study Description: The study has 5 components:

Phase 1

- Monotherapy Dose Escalation
- Monotherapy Expansion
- Combination Dose Escalation

Phase 2

- Monotherapy Phase 2
- Combination Phase 2

Objectives: Primary Objectives:

Phase 1

- Monotherapy Dose Escalation: Determine a maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) for ZN-c5 as a monotherapy
- Monotherapy Expansion: Investigate the safety and tolerability of ZN-c5 as a monotherapy in subjects with Estrogen Receptor (ER) positive, Human Epidermal Growth Factor Receptor-2 (HER2) negative advanced breast cancer
- Combination Dose Escalation: Determine an MTD or RP2D for ZN-c5 when administered in combination with palbociclib

Phase 2

- Monotherapy Phase 2: Determine preliminary anti-tumor efficacy (Clinical Benefit Rate [CBR]) for ZN-c5 as a monotherapy
- Combination Phase 2: Determine preliminary anti-tumor efficacy (CBR) for ZN-c5 when administered in combination with palbociclib

Secondary Objectives:

- Monotherapy Dose Escalation and Monotherapy Phase 2: Investigate the safety and tolerability of ZN-c5 as a monotherapy in subjects with ER positive, HER2 negative advanced breast cancer
- Combination Dose Escalation and Combination Phase 2: Investigate the safety and tolerability of ZN-c5 in combination with palbociclib in subjects with ER positive, HER2 negative advanced breast cancer

- Monotherapy Expansion Phase 1: Investigate the preliminary anti-tumor efficacy (CBR) for ZN-c5 as a monotherapy
- All Cohorts: Assess preliminary efficacy of ZN-c5 alone and in combination with palbociclib by Objective Response Rate (ORR), CBR, Duration of Response (DOR), Progression-Free Survival (PFS) and Overall Survival (OS) using Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) as assessed by investigators
- Monotherapy Dose Escalation and Monotherapy Expansion Phase 1 and Monotherapy Phase 2: Characterize the pharmacokinetics (PK) of ZN-c5 (and its potential metabolites as applicable) when given as oral monotherapy
- Combination Dose Escalation and Combination Phase 2: Characterize the PK of ZN-c5 (and its potential metabolites as applicable) when given in combination with palbociclib
- Combination Dose Escalation and Combination Phase 2: Characterize the PK of palbociclib when given in combination with ZN-c5

Tertiary/Exploratory Objectives (All Cohorts):

- Evaluate pharmacodynamic and prognostic biomarkers associated with disease prognosis and/or likelihood of response to ZN-c5
- Assess the effect of ZN-c5 on tumor's ability to bind estradiol as measured by uptake of ^{18}F-fluoroestradiol (FES) Positron Emission Tomography (PET)

Endpoints:

Primary Endpoints:

- Monotherapy Dose Escalation and Combination Dose Escalation: Observed Dose Limiting Toxicities
- Monotherapy Expansion: Safety and tolerability as measured by incidence of treatment-emergent adverse events (TEAEs) and lab abnormalities
- Monotherapy Phase 2 and Combination Phase 2: CBR (CR [+ PR] + SD ≥ 24 weeks). PR will only be included for patients with measurable disease.

Secondary Endpoints:

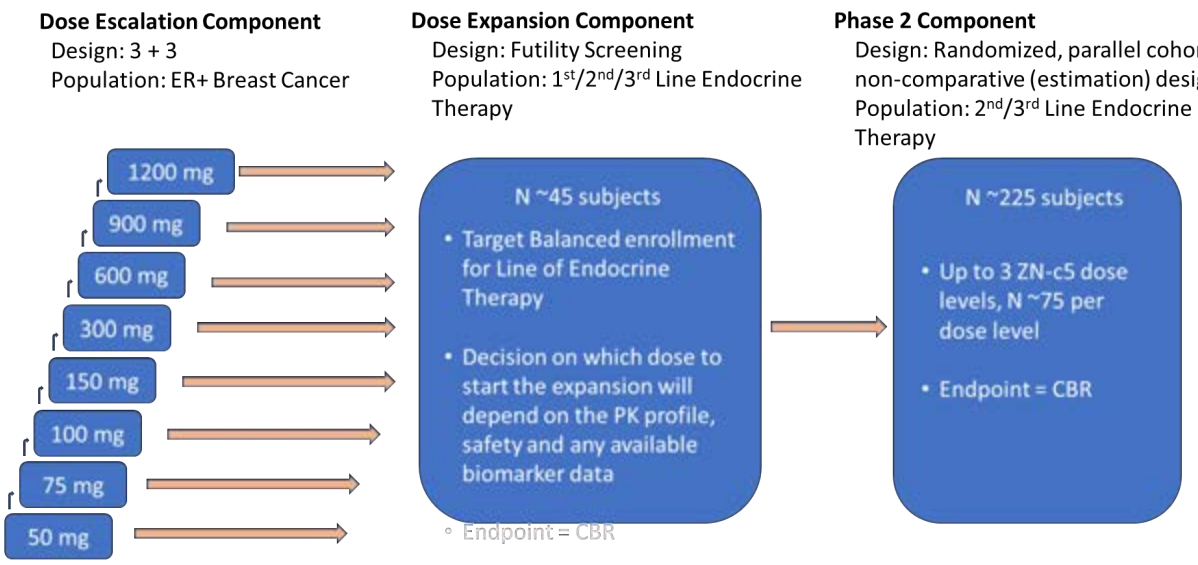
- All Cohorts: Safety and tolerability as measured by incidence of treatment-emergent AEs and lab abnormalities
- Monotherapy Expansion: CBR (CR [+ PR] + SD ≥ 24 weeks). PR will only be included for patients with measurable disease.

	• All Cohorts: Tumor response including ORR, DOR, CBR, PFS using Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) as assessed by Investigators, and OS • All Cohorts: ZN-c5 (and its potential metabolites as applicable) and palbociclib (if applicable) plasma pharmacokinetic (PK) parameters (including C_{max}, T_{max}, AUC_{last}, $t_{½}$ and C_{tau}, as applicable) Tertiary/Exploratory Endpoints (All Cohorts): • Pharmacodynamic or prognostic markers (including but not limited to estrogen receptor degradation, Ki-67, RNA-Seq, 4βhydroxycholesterol/cholesterol and ESR1 mutations) • FES-PET Scan (^{18}F-fluoroestradiol radiotracer)
Study Population:	Phase 1 Monotherapy Dose Escalation and Combination Dose Escalation: Adult subjects with advanced ER+/HER2-negative advanced breast cancer who are refractory to or intolerant of established therapy(ies) known to provide clinical benefit for their malignancy. Phase 1 Monotherapy Expansion: Adult subjects with advanced ER+/HER2-negative advanced breast cancer who have received up to 2 prior lines of endocrine-based therapy for advanced/metastatic breast cancer. Phase 2 Monotherapy: Adult subjects with advanced ER+/HER2-negative breast cancer who have received 1 or 2 prior lines of endocrine-based therapy for advanced/metastatic breast cancer. Phase 2 Combination: Adult subjects with advanced ER+/HER2-negative breast cancer who have received up to 1 prior line of endocrine-based therapy for advanced/metastatic breast cancer.
Phase:	1/2
Estimated No. of Sites:	Approximately 60 centers globally, including the US
Estimated No. of Subjects:	Phase 1 Monotherapy Dose Escalation: Approximately 36 subjects Phase 1 Monotherapy Expansion: Approximately 45 subjects Phase 1 Combination Dose Escalation: Approximately 40 subjects Phase 2 Monotherapy: Approximately 225 subjects Phase 2 Combination: Approximately 112 subjects ESTIMATED TOTAL: Approximately 458 subjects
Study Intervention:	ZN-c5 Palbociclib (IBRANCE®); Pfizer, Inc.
Overall Study Design:	Phase 1/2 trial of ZN-c5 both as monotherapy and in combination with palbociclib. The study consists of **5 components**: **Phase 1 Monotherapy Dose Escalation** and **Phase 1 Monotherapy Expansion**: Single agent ZN-c5 will be evaluated at sequentially escalating doses starting with 50 mg and up to 1200 mg administered orally, once daily

	(alternatively, this total daily dose may be divided by 2 and administered BID [every 12 hours]), using a 28-day cycle (Dose Escalation). During or on completion of the Dose Escalation, additional patients may be enrolled onto one or more dose levels for the Monotherapy Expansion portion of the study. The decision to expand will be based on the PK, safety and available biomarker data. **Phase 2 Monotherapy**: ZN-c5 will be administered at the single agent RP2D and schedule. This Monotherapy Phase 2 portion will follow a randomized, parallel cohort, non-comparative (estimation) design and up to 3 dose levels of ZN-c5 will be assessed. **Phase 1 Combination Dose Escalation** and **Phase 2 Combination**: In Phase 1, ZN-c5, starting at a dose level deemed well-tolerated (as determined from the Monotherapy Dose Escalation) will be evaluated in combination with palbociclib in ascending dose cohorts to assess the safety and determine the MTD or RP2D. ZN-c5 will be administered orally once daily (alternatively, this total daily dose may be divided by 2 and administered BID [every 12 hours]), on a 28-day treatment cycle. In Phase 2 Combination, ZN-c5 will be dosed at the RP2D and potentially at a lower dose level in combination with palbociclib. The lower ZN-c5 dose will be selected based on available safety, PK and biomarker data. The dose and schedule of palbociclib will be the Regulatory Authority's approved dose of 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment (1 cycle of treatment = 28 days) for both the Phase 1 Combination Dose Escalation and Phase 2 components of the study. During the Dose Escalation, additional patients may be enrolled onto one or more dose levels (backfill). The Combination Phase 2 will follow a randomized, parallel group, non-comparative design, assuming both the RP2D and the lower dose are investigated, or a single dose cohort design, if only the RP2D is investigated. Each dose cohort will follow a Simon 2-stage design.
Study Duration:	60 months
Participant Duration:	Treatment will continue in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reason (specified in Section 7.2).

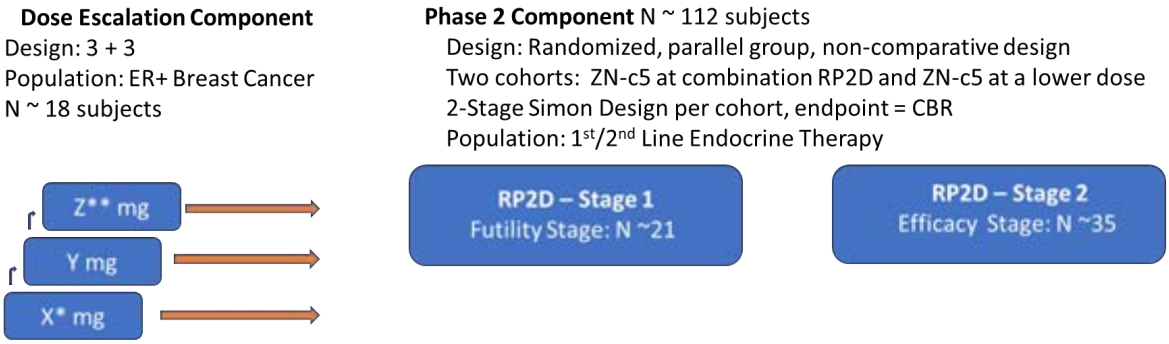
1.2 SCHEMA

Figure 1 ZN-c5-001 Phase 1 Monotherapy Dose Escalation, Expansion and Phase 2



The dose in mg is the total dose/day

Figure 2 ZN-c5-001 Phase 1 Combination with Palbociclib Dose Escalation and Phase 2



* Decision on which ZN-c5 dose to start the expansion will depend on the PK profile, safety and any available biomarker data
** More than 3 ZN-c5 dose levels may be assessed based on the Monotherapy Dose Escalation
Palbociclib is dosed at 125 mg/day taken orally once daily for 21 consecutive days, followed by 7 days off treatment to comprise a complete cycle of 28 days.

1.3 SCHEDULE OF ACTIVITIES

Table 1: Study Procedures Table

Study Phase	**Screening**	**Cycle 1 (28-day cycle)**					**Cycles ≥ 2 (28-day cycle)**		**EOT**	**30-day Safety Follow-up**	**Disease Assessment Follow-up[21] (every 12 weeks)**	**Survival Follow-up[22] (every 12 weeks)**
Cycle Day	**Day -28**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 16**	**Day 1**	**[Day 15* Cycle 2 Combination only]**				
Window (days)	**-28 to -1**			**± 1**	**± 2**		**[± 4[23]]**	**[± 2]**	**± 7**	**± 7**	**± 7**	**± 14**
Informed Consent	X											
Medical and Medication History[1]	X											
Physical Examination[2]	X	X		X	X		X	[X]	X	X		
ECOG Performance Status	X	X					X	[X]	X	X		
Vital Signs[3]	X	X		X	X		X	[X]	X	X		
Triplicate 12-lead ECG[4]	X	X	[X]		X	[X]	[X]		X			
Adverse events/ Concomitant medications[5]	[X]	X	[X]	X	X	[X]	X	[X]	X	X		
Enrollment	X											
Hematology	X[7]	X		X	X		X	[X]	X	X		
Chemistry	X[7]	X		X	X		X	[X]	X	X		
Coagulation[8]	X[7]								X			
Full Lipid Panel[9]		[X]					[X]					
Urinalysis[10]	X[7]								X			
Pregnancy Test[11]	X	X					X		X	X		
PK[12]		[X]	[X]	[X]	[X]	[X]	[X]					

Study Phase	**Screening**	**Cycle 1 (28-day cycle)**					**Cycles ≥ 2 (28-day cycle)**		**EOT**	**30-day Safety Follow-up**	**Disease Assessment Follow-up[21] (every 12 weeks)**	**Survival Follow-up[22] (every 12 weeks)**
Cycle Day	**Day -28**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 16**	**Day 1**	**[Day 15* Cycle 2 Combination only]**				
Window (days)	**-28 to -1**			**± 1**	**± 2**		**[± 4[23]]**	**[± 2]**	**± 7**	**± 7**	**± 7**	**± 14**
ZN-c5 pharmaco-dynamic and exploratory biomarkers in blood[13]		X					X		[X]		[X]	
Tumor Biopsy[14]	[X]						[X]		[X]		[X]	
ESR1 Mutation[15]		X					X		[X]		[X]	
CT/MRI[16]	X						X		X		[X]	
4β-hydroxycholesterol / cholesterol[17]		X			X		X					
FES-PET[18]	[X]						[X]					
ZN-c5 oral dosing[19]		X										
Palbociclib oral dosing (Combo only)[20]		[X]										
Subject Dosing Diary Accountability and/or Dispensing[6]		X					X		X			
LTFU[22]												[X]

Notes: X = Required; [X] = Only applicable as per footnote as indicated by the Assessment
Cycle 1 Day 1 safety lab samples, physical examination, ECOG status and pregnancy test may be assessed up to 3 days prior to the Day 1 visit. On subsequent visits throughout the study, these procedures/assessments are allowed to be performed within 1 day prior to the planned visit.
Cycle 1 Days 2 and 16 are only required for subjects participating in the Phase 1 parts of the protocol.
*Cycle 2 Day 15 visit – only for subjects participating in Combination Therapy (Combination Dose Escalation and Phase 2)

1. Medical history includes significant past medical events (e.g., prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

2. Screening and End of Treatment Physical Examinations (PE) will be a complete PE. Beginning at C1D1, a modified physical examination may be performed. Weight (without shoes) should be measured at each PE. Height (without shoes) is measured at Screening only.
3. C1D1 Vital Signs will be taken within 15 min pre-ZN-c5 dose and 2 and 4 hours post-dose (Phase 1) or pre-dose and 2 hours post-dose (Phase 2); vital signs will be taken pre-dose only at all subsequent visits. Oxygen saturation will be tested with a pulse oximeter.
4. Resting, semi recumbent triplicate ECGs will be collected at any time during Screening window, Day 1 of every other cycle (alternating cycles) starting with Cycle 2 (at pre-dose), and at EOT. In Phase 1, triplicate ECGs will be collected on C1D1 and C1D15 at pre-dose, 8 hours, and 24 hours post-dose (pre-dose on C1D2 and C1D16). In Phase 2, triplicate ECGs will be collected on C1D1 and C1D15 at pre-dose and 2 hours post-dose. ECGs should preferably be collected prior to PK (or any other blood draw) if they are to be collected at the same nominal time point. ECGs should be collected over a 5-minute window at each time point.
5. AEs will be assessed using NCI CTCAE (v 4.03) criteria. Subjects will also return to clinic at 30-days (± 7 days) post last IP dose (but prior to initiation of subsequent breast cancer therapy) to assess AEs and SAEs. At Screening, all medications taken up to 30 days prior to Screening will be documented in the eCRF.
6. Subjects will be given a Subject Diary on which they will record dates/times of study drug administration. Compliance with study drug(s) will be assessed and reviewed during visits.
7. Screening chemistry, hematology, coagulation, and urinalysis should be collected within 7 days of C1D1.
8. Coagulation assessment includes PT/INR, aPTT.
9. A non-fasting full lipid panel will be performed on C1D1, C3D1 (coinciding with the first on-study tumor assessment after 8 weeks) and C7D1 (6 months into the study). This will not be collected in the Monotherapy Phase 2.
10. Urinalysis assessment includes visual inspection, microscopic examination, and dipstick test for pH, protein, glucose, WBC, bilirubin, and blood.
11. Serum pregnancy testing will be conducted at Screening (within ≤ 7 days of C1D1). Serum or urine pregnancy tests thereafter will be done on Day 1 of every cycle for all premenopausal and perimenopausal female subjects of childbearing potential, including EOT and the Safety Follow-up Visit.
12. Plasma samples for PK analysis of ZN-c5 (having been administered without food [at least 1 hour before and 2 hours after a meal]) and of palbociclib (having been administered with food) will be collected relative to ingestion of each drug as per Table 6 and Table 7. Regarding the PK sampling for ZN-c5 if administered twice daily (BID), a sample at 12 hours post morning dose and immediately preceding the second daily dose may also be collected (optional). Note: If the optional, On-Treatment tumor biopsy is performed, an additional PK sample should be collected at that time.
13. Whole blood, serum and/or plasma will be collected for exploratory biomarkers at C1D1, C2D1, and at time of disease progression.
14. Tumor biopsy: At baseline, *de novo* biopsy of any amenable site of disease (at investigator's discretion). Additional tumor biopsy at C2D1 or any time beyond may also be obtained. The on-treatment biopsy should be obtained 2 – 4 hours after the subject has taken the ZN-c5 dose that day. Subjects will also have the option to undergo a biopsy of a lesion at the time of disease progression. Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual. Any residual tumor remaining after analysis may be used for exploratory research into factors that may influence development of breast cancer and/or response to ZN-c5. All tumor biopsies are optional for all subjects participating during the study. Biopsies must not be taken from target lesions used to assess anti-tumor efficacy, if possible. If sufficient tumor material is available, part of the tumor biopsy at C2D1 will be used for determination of ZN-c5 tissue concentration. If a biopsy is obtained on C2D1 or beyond, a plasma PK sample should also be collected, as close as possible, within 2 hours prior to the biopsy.
15. A blood sample for the assessment of ESR1 mutations will be drawn at C1D1, C2D1, and at time of progression.
16. Tumor evaluation by CT/MRI or applicable scan will be performed during Screening (within 28 days of Cycle 1 Day 1) and every 8 weeks (± 7 days) after C1D1 for the first 24 weeks. After 24 weeks, scans may be performed every 12 weeks (± 7 days). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. Applicable scans to be done at EOT visit if not done within the previous 4 weeks.
17. Plasma samples for 4β-hydroxycholesterol and cholesterol will be collected pre-dose on C1D1, C1D15, and pre-dose on Day 1 of Cycles 2-4 of the Monotherapy Dose Escalation and Expansion.
18. A FES-PET scan (optional) should be conducted at Screening and at least after 1 month of treatment (preferably within the first 2 months, in Cycle 2).
19. Beginning on C1D1, subjects will take ZN-c5 once daily (alternatively, this total daily dose may be divided by 2 and administered BID [every 12 hours]). ZN-c5 dosing and administration as per assigned cohort (see Section 6.1.2.1).
20. In Phase 1, beginning on C1D1, subjects in the combination treatment cohorts will take palbociclib at the label indicated dose of 125 mg orally once daily (2 hours after the ZN-c5 dose was taken) for 21 consecutive days followed by 7 days off treatment (1 cycle of treatment = 28 days) (see Section 6.1.2.2). In Phase 2, subjects in the combination treatment cohorts will take palbociclib at the label indicated dose of 125 mg orally once daily (at the same time the ZN-c5 dose is taken) for

21 consecutive days followed by 7 days off treatment (1 cycle of treatment = 28 days).21. Disease Assessment Follow-up Visit: Subjects without progression of disease (PD) at the time of study drug discontinuation will continue to undergo disease evaluations every 12 weeks ± 7 days until confirmation of PD, initiation of the first subsequent cancer therapy, withdrawal of consent, death, loss to follow-up, or until the study is terminated. Once a subject has confirmation of PD or has initiated subsequent cancer therapy, whichever occurs first, disease follow-up will discontinue.

22. Long-term Follow-up (LTFU) – Subjects will be contacted every 3 months (phone or medical records) for survival status and collection of subsequent breast cancer treatments.
23. In the Combination Dose Escalation and Combination Phase 2 with palbociclib, the window for the Day 1 visit for subsequent cycles is only + 4 days, since there must always be at least a full 7-day off treatment recovery period for palbociclib before starting the next 21-day dosing cycle.

2 INTRODUCTION

2.1 STUDY RATIONALE

Hormone receptor-positive, HER2-negative breast cancer is the most common subset of breast cancer, with the majority of patients diagnosed at an early stage and remaining relapse-free if treated with a prolonged course of endocrine therapy[1]. Unfortunately, not all patients respond to first-line endocrine therapy, and many patients who initially respond will relapse (acquired resistance). Approximately one-third of all HR+/HER2-negative patients diagnosed with initial early stage disease experience disease recurrence[2], resulting in the HR+/HER2-negative subset accounting for the majority of breast cancer related deaths. The estrogen receptor (ER) in these patients is a key driver of disease progression, and the primary reason for relapse in these patients is that endocrine therapies are only partially effective, typically causing cell cycle arrest rather than cell death. As a result, secondary resistance to endocrine therapy is a major clinical challenge.

Most pre- or peri-menopausal women with HR+ breast cancer present with early stage disease and are treated with the anti-estrogen tamoxifen (with or without ovarian ablation by surgery, chemotherapy or luteinizing hormone-releasing hormone) in the adjuvant setting[3]. Upon initial presentation with metastatic disease during pre-menopause, the recommended approach is to suppress ovarian function (by ovarian ablation or luteinizing hormone-releasing hormone (LHRH) agonist therapy), and then follow post-menopausal treatment guidelines, switching treatment from tamoxifen to AIs or fulvestrant. Thus, in clinical practice so called “pre/peri-menopausal” patients with HR+ metastatic breast cancer will be rendered postmenopausal by the time of first line treatment for advanced disease.

Upon disease progression on hormonal therapy, treatment options have historically been limited to a change in AIs (steroidal or nonsteroidal) or the use of the ER antagonists such as fulvestrant. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER-positive tumors. While effective, more efficacious and safe therapeutic options are still needed, particularly in selected patient populations. Thus, HR+/HER2-negative breast cancer patients who have tumor progression following endocrine therapies for advanced/metastatic disease remains an important medical need.

Fulvestrant is currently the only approved anti-estrogen drug that binds and selectively degrades the ER. Recent data with fulvestrant administered at the dose of 500 mg/monthly to patients with recurrent HR+/HER2-negative breast cancer indicate significant anti-tumor activity after both anti-estrogen and aromatase inhibitor (AI) failures. Fulvestrant is currently indicated for the treatment of postmenopausal women with metastatic HR+ breast cancer following the failure of antiestrogen therapy. Although it is effective, fulvestrant is limited by its poor pharmaceutical properties, which leads to sub-optimal exposure due to its administration via intramuscular injection, which also results in potential injection-related adverse events such as hypersensitivity reactions, including urticaria and angioedema. In addition, as with other intramuscular injections, caution is advised when treating patients with bleeding disorders or thrombocytopenia, and those receiving treatment with anticoagulants such as warfarin. Therefore, efforts have been made to develop selective ER-receptor degraders that can be taken by mouth to avoid some potential complications of injection and increase the exposure.

Fulvestrant has also not been studied extensively in pre-or peri-menopausal women, although it is expected to also add benefit to the treatment of these patients (if given concurrently with ovarian suppression/ablation). Clinical experience demonstrates that medical or surgical ovarian ablation produces comparable outcomes to tamoxifen monotherapy and supports the use of goserelin (LHRH agonist) concurrently with fulvestrant in premenopausal women with metastatic breast cancer[4]. Clinical studies are currently underway evaluating the combination of fulvestrant with medical ovarian suppression in premenopausal women with breast cancer[5].

There is evidence to suggest that more complete estrogen receptor degradation may result in improved clinical outcomes. Therefore, this study will investigate the safety and potential efficacy of an oral selective estrogen receptor degrader in the hormone-therapy refractory ER+/HER2-negative patient population.

The use of a selective estrogen receptor degrader (SERD) in combination with CDK4/6 inhibition was shown to be clinically beneficial in a large, multinational clinical trial PALOMA-3, which combined fulvestrant with palbociclib (IBRANCE®, Pfizer Inc.) in patients with HR-positive, HER2-negative advanced or metastatic breast cancer who had disease progression on or after prior adjuvant or metastatic endocrine therapy[6]. PALOMA-3 was an international, randomized, double-blind, parallel group, multicenter study of palbociclib (IBRANCE) plus fulvestrant versus placebo + fulvestrant conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy. A total of 521 pre/postmenopausal women were randomized 2:1 to palbociclib + fulvestrant or placebo + fulvestrant and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of study. Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed Progression-Free Survival (PFS) evaluated according to RECIST 1.1.

Patients enrolled in the PALOMA-3 study had a median age of 57 years (range 29 to 88). The majority of patients on study were White (74%), all patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy, and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the Investigator-assessed PFS analysis showed a statistically significant improvement in PFS (9.5 months vs. 4.6 months) in favor of palbociclib + fulvestrant. Consistent results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. The Overall Survival (OS) data were not mature at the time of the final PFS analysis. These results suggest that the combination of a SERD and a CDK4/6 inhibitor are a clinically useful strategy for the treatment of ER+/HER2-negative advanced breast cancer patients after endocrine therapy failure.

2.2 BACKGROUND

ZN-c5 (also known as KP-868) binds potently to the estrogen receptors alpha and beta (ERα and ERβ) with K_i values of 3.4, 3.2 nM, respectively. Treatment of MCF-7 cells with ZN-c5 results in the degradation of ERα (EC_{50} = 0.19 nM) and inhibition of breast cancer cell growth (MCF-7, IC_{50} = 0.4 nM, MCF-7 LTED IC_{50} = 0.2 nM). ZN-c5 is orally bioavailable and shows improved activity over fulvestrant in human tumor xenograft models and shows activity in tumor models that are resistant to tamoxifen. In the MCF-7 orthotopic tumor xenograft model, ZN-c5 treatment at 5 mg/kg and 10 mg/kg, resulted in 89% and 101% tumor growth inhibition (TGI), respectively, as a single agent. The 5 mg/kg dose resulted in 89% TGI and 9.35 µg*hr/m is considered the minimal efficacious exposure for ZN-c5. Combination of ZN-c5 with the CDK inhibitors palbociclib or abemaciclib, resulted in increased tumor growth inhibition and regression of large tumors. In the tamoxifen resistant (TAMR) MCF-7 orthotopic tumor model, treatment with ZN-c5 at 10 and 40 mg/kg resulted in 37% and 60% TGI, respectively. In rat uterine wet weight studies, ZN-c5 acted as an estrogen antagonist but not an agonist. Overall these studies show that ZN-c5 is a novel and potent SERD with oral bioavailability and strong activity in estrogen-dependent and tamoxifen-resistant tumor models.

Nonclinical in vivo data indicate that ZN-c5 is rapidly absorbed with oral bioavailability typically exceeding 74% in all species. ZN-c5 plasma exposure was generally dose proportional with no major accumulation occurring in the 28-day and 13-week toxicology studies. Sex differences in ZN-c5 exposure in rats was observed, consistent with CYP3A and CYP2C metabolism of ZN-c5 as shown in an in vitro CYP phenotyping study. Free fraction of ZN-c5 was 0.241% in human plasma, ~0.5% in rodents and ~0.15% in dogs. ZN-c5 shows an efflux ratio of < 1 in Caco-2 cells and does not appear to be a P-gp or BCRP, substrate.

ZN-c5 is metabolically stable in liver microsomes and hepatocytes of all species tested except monkeys. CYP isoforms that most efficiently metabolize ZN-c5 are CYP3A5, CYP2C9, and CYP3A4. The major metabolite was detected in liver microsomes and hepatocytes of all species tested except mice. ZN-c5 inhibited CYP2C8 with an IC_{50} value of 0.152 µM. The IC_{50} values for the other CYP isoforms ranged from 20.9 to > 50 µM. No time dependent inhibition of CYP3A was observed. ZN-c5 did not inhibit P-gp, whereas, the IC_{50} value for BCRP inhibition was 1.56 µM. IC_{50} values for SLC transporter inhibition ranged from 1.42 to > 30 µM with OATP1B1 and OATP1B3 being most potently inhibited (1.42 and 5.80 µM, respectively). IC_{50} value for BSEP inhibition was 20.2 µM. In a CYP induction experiment performed in hepatocytes from three human donors, there was no CYP1A2 and CYP2B6 induction but CYP3A4 induction was observed in all three donors. Subsequently, PBPK modeling was performed with the objectives to develop a model for ZN-c5 using in vitro ADME, physicochemical and relevant clinical data to predict its Drug-Drug Interaction (DDI) liability with substrates of CYP3A4, CYP2C8, P-gp, BCRP and OATP1B1. Simulations predicted a moderate interaction with CYP3A4 substrates, a mild to moderate interaction with CYP2C8 substrates, a minimal interaction with either P-gp or OATP1B1 substrates and a potential for a moderate BCRP-mediated interaction (the latter considered exploratory). Overall, ZN-c5 may alter clearance and exposure of concomitantly administered drugs that are substrates of CYP2C8, CYP3A4, and, potentially, BCRP.

The results of an excretion study conducted in female rats that received a single IV or oral dose of ZN-c5 indicate that ZN-c5 is eliminated from the body by biliary excretion, and renal elimination is not substantial.

The nonclinical safety profile of ZN-c5 has been well characterized through the conduct of single- and repeat-dose studies of up to 13 weeks in duration. The primary target organ effects in repeat dose studies were related to reproductive tissues and the liver. Microscopic findings in the bone marrow in high-dose treated dogs in the 28-day study consisted of decreased erythropoiesis which correlated with the hematology finding of decreased reticulocyte counts, secondary to inflammation. These effects were not seen in the 13-week repeat dose dog study. The liver effect in the 28-day dog study was associated with cholestasis leading to hyperbilirubinemia, most likely due to inhibition of the bile salt export pump (BSEP) in vitro, with an IC_{50} of 20.2 µM. These liver effects were not observed in the 13-week dog study. In the 14-day rat study, the liver effects were limited to microvesicular changes due to lipid deposition in hepatocytes as confirmed with oil--red--O staining. This effect in rats is most likely due to the anti-estrogenic effect of ZN-c5 given that estrogen plays an important role in lipid homeostasis within the liver. Effects of ZN-c5 on sex organs (decreased uterine weights, development of ovarian cysts, hypertrophy and hyperplasia of the mammary gland, prostate atrophy, testicular degeneration) are postulated to also be due to the pharmacological effect of the test article. This includes the effects seen in the male dog testes. The non-glandular stomach changes noted in the rat are not a risk to humans as humans lack a non-glandular stomach. The potential for reversibility of all adverse effects was established following a 1-month non-dosing period. All the adverse effects reversed or showed evidence of reversibility, except for the testicular effects in dogs that did not exhibit any signs of recovery.

In the safety pharmacology endpoints captured during the repeat dose toxicology studies, ZN-c5 did not exhibit any adverse CNS effects based on the functional observation battery (FOB), and no respiratory findings in the repeat dose toxicology studies or in a stand-alone respiratory study. In addition, there were no cardiovascular effects based on monitoring of electrocardiogram (ECG) parameters in the 28-day dog study or in a definitive cardiovascular study in dogs with telemetry implants. In addition, ZN-c5 was negative in the in vitro and in vivo genetic toxicology studies.

The nonclinical safety findings related to ZN-c5 administration represent toxicities that can be monitored and are considered clinically manageable or acceptable risks in the intended patient population. The nonclinical safety profile of ZN-c5 has been adequately characterized to support progression into clinical trials in advanced cancer patients.

Please refer to the ZN-c5 Investigator's Brochure (IB) for additional information.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Based on the nonclinical toxicology studies conducted with ZN-c5, the potential adverse effects will include alterations in sex organs, the potential for hepatic injury, and a potential decrease in erythropoiesis/reticulocytes. The sex organ effects (including but not limited to development of ovarian cysts, atrophy of the uterus, and hypertrophy and hyperplasia of the mammary gland) are due to

decreases in estrogen as a result of ZN-c5 pharmacology. Although specific nonclinical fertility studies have not been conducted with ZN-c5, based on the microscopic changes in the testes and ovaries, decreased fertility in both male and female patients taking ZN-c5 is possible. The potential hepatic effects include cholestasis and hyperbilirubinemia leading to hepatocellular necrosis, as well as pruritus due to elevated bile salts. All changes, except for the changes in the testes, were noted to be reversible during a treatment-free recovery period. The adverse effect profile of fulvestrant is well-documented, and includes injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremities, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation, as well as increased hepatic enzymes.

The adverse effect profile of palbociclib (IBRANCE®, Pfizer Inc.) is well-documented across multiple international, multi-center trials. Known adverse effects attributable to palbociclib include low blood cell counts (cytopenia), fatigue, nausea, diarrhea, vomiting, infections, stomatitis, alopecia, rash, decreased appetite, asthenia, and pyrexia, among other potential adverse effects. The full product safety information is available in the most recent Prescribing Information for palbociclib from Pfizer.

2.3.2 KNOWN POTENTIAL BENEFITS

Pre-clinical data suggests that treatment with ZN-c5 can result in anti-proliferative activity in ER+ tumor models, and clinical data has shown that the combination of a SERD and a CDK4/6 inhibitor is clinically beneficial in patients with ER+/HER2-negative advanced breast cancer who have progressed on or after endocrine therapy.

For patients enrolled in the combination therapy portion of the trial, subjects will receive palbociclib (IBRANCE®, Pfizer Inc.), which has been approved by Regulatory Authorities for the treatment of HR+, HER2 negative advanced or metastatic breast cancer in combination with an AI or fulvestrant based on significant improvement in Progression-Free Survival (PFS).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This study is a Phase 1/2 study with ZN-c5, an oral selective estrogen receptor degrader, alone and in combination with the CDK4/6 inhibitor palbociclib. The selected starting dose for this study is within the range that is predicted to provide biological activity based upon nonclinical explant models, in accordance with the ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. The toxicological profile of ZN-c5 has been evaluated in rats and dogs in studies of up to one month in duration. The pre-clinical safety profile has not identified any risks that would preclude investigation in this setting. The study is designed to minimize potential risks, and close monitoring is in place for those risks deemed to be most likely or serious.

The investigation of ZN-c5 alone and in combination with the approved agent palbociclib in this patient population appears reasonable, based upon the pre-clinical safety profile, preliminary signals of efficacy, the proven efficacy of mechanism of action, and the strength of the scientific hypothesis under evaluation. Thus, the benefit/risk assessment for this first-in-human Phase 1/2 study supports the oral administration of ZN-c5 to subjects with advanced ER+/HER2-negative breast cancer alone and in combination with palbociclib, according to the proposed study design.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION
Primary		
Phase 1 • Monotherapy Dose Escalation: Determine a maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) for ZN-c5 as a monotherapy • Monotherapy Expansion: Investigate the safety and tolerability of ZN-c5 as a monotherapy in subjects with Estrogen Receptor (ER) positive, Human Epidermal Growth Factor Receptor-2 (HER2) negative advanced breast cancer • Combination Dose Escalation: Determine an MTD or RP2D for ZN-c5 when administered in combination with palbociclib	Observed Dose Limiting Toxicities Safety and tolerability as measured by incidence of treatment-emergent AEs and lab abnormalities Observed Dose Limiting Toxicities	This is accepted methodology to evaluate safety and determine the doses for further evaluation. The incidence of treatment emergent AEs and lab abnormalities reflects the safety profile of ZN-c5.
Phase 2 • Monotherapy Phase 2: Determine preliminary anti-tumor efficacy (Clinical Benefit Rate [CBR]) for ZN-c5 as a monotherapy • Combination Phase 2: Determine preliminary anti-tumor efficacy (CBR) for ZN-c5 when administered in combination with palbociclib	CBR (CR [+ PR] + SD ≥ 24 weeks). PR will only be included for patients with measurable disease.	ZN-c5 is expected to have activity in the selected patient population, and standard measures of disease response/progression were chosen to evaluate potential efficacy.
Secondary		
• Monotherapy Dose Escalation and Phase 2: Investigate the safety and tolerability of ZN-c5 as a monotherapy in subjects with ER positive, HER2-negative advanced breast cancer • Combination Dose Escalation and Phase 2: Investigate the safety and tolerability of ZN-c5 in combination with palbociclib in subjects with ER positive, HER2 negative advanced breast cancer	All Cohorts: Safety and tolerability as measured by incidence of treatment-emergent AEs and lab abnormalities	The incidence of treatment-emergent AEs and lab abnormalities reflects the safety profile of ZN-c5 across all subjects in the study.

OBJECTIVES	ENDPOINTS	JUSTIFICATION
• Monotherapy Expansion Phase 1: Investigate the preliminary anti-tumor efficacy (CBR) for ZN-c5 as a monotherapy • All Cohorts: Assess preliminary efficacy of ZN-c5 alone and in combination with palbociclib by Objective Response Rate (ORR), CBR, Duration of Response (DOR), Progression-Free Survival (PFS) and Overall Survival (OS) using Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) as assessed by investigators	CBR (CR [+ PR] + SD ≥ 24 weeks). PR will only be included for patients with measurable disease. Tumor response including ORR, DOR, CBR, PFS using Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) as assessed by Investigators, and OS	ZN-c5 is expected to have activity in the selected patient population, and standard measures of disease response/progression were chosen to evaluate potential efficacy.
• Monotherapy Dose Escalation, Phase 2 and Expansion: Characterize the pharmacokinetics (PK) of ZN-c5 (and its potential metabolites as applicable) when given as oral monotherapy • Combination Dose Escalation and Phase 2: Characterize the PK of ZN-c5 (and its potential metabolites as applicable) when given in combination with palbociclib • Combination Dose Escalation and Phase 2: Characterize the PK of palbociclib when given in combination with ZN-c5	ZN-c5 (and its potential metabolites as applicable) and palbociclib (if applicable) plasma PK parameters (including C_{max}, T_{max}, AUC_{last}, $t_{½}$ and C_{tau}, as applicable)	ZN-c5/palbociclib plasma pharmacokinetic parameters may allow for correlating exposure with toxicity or efficacy.
Tertiary/Exploratory (All Cohorts)		
• Evaluate pharmacodynamic and prognostic biomarkers associated with disease prognosis and/or likelihood of response to ZN-c5	Pharmacodynamic or prognostic markers (including but not limited to estrogen receptor degradation, Ki67, RNA seq, 4β hydroxycholesterol/ cholesterol and ESR1 mutations	Investigational pharmacodynamics may allow for correlation between response and biomarkers

OBJECTIVES	ENDPOINTS	JUSTIFICATION
• Assess the effect of ZN-c5 on tumor's ability to bind estradiol as measured by uptake of ^{18}F-fluoroestradiol (FES) positron emission tomography (PET)	FES-PET Scan (^{18}F-fluoroestradiol radiotracer)	PET scanning with FES correlates with ER expression. It is performed to explore its potential as a predictive assay and method of assessing pharmacodynamic response to ZN-c5.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1/2, open-label, multicenter, dose-escalation and expansion study to evaluate the safety, tolerability, PK, and preliminary efficacy of ZN-c5 administered orally in subjects with advanced ER+/HER2-negative breast cancer, both as monotherapy and in combination with palbociclib (IBRANCE®, Pfizer Inc.).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Open label dose escalation with a standard rule-based 3+3 design was chosen so as to accurately identify the MTD/RP2D as safely as possible, while minimizing the number of subjects exposed to lower (and potentially less efficacious) doses of study drug. For the combination portion of the study, dose escalation will start and will follow ZN-c5 dose levels that are deemed to be well-tolerated in the Monotherapy Dose Escalation. ZN-c5 will be evaluated in combination with the approved dose of palbociclib in ascending dose cohorts to assess the safety and determine the MTD or RP2D prior to initiation of the Phase 2 portion of the study.

Screening (estimation) as well as Simon 2-stage designs are well established to evaluate anti-tumor efficacy in the uncontrolled proof of concept setting, considering that no previous clinical efficacy experience exists in this setting. It accounts for minimal subject exposure in the event of futile efficacy against historically established performance in a specific population setting.

4.3 JUSTIFICATION FOR DOSE

The recommended clinical starting dose (50 mg) in advanced cancer patients is based on the 28-day repeat-dose toxicity study in dogs, with the highest non-severely toxic dose (HNSTD) at 10 mg/kg/day. Taking one-sixth the HNSTD dose as outlined in ICH S9, then correcting for body surface area, equates to a recommended starting dose of 0.93 mg/kg, or 55.6 mg for a 60 kg patient. Therefore, a 50 mg starting dose was suggested as the safe starting dose for the Phase 1 Monotherapy Dose Escalation study.

In the ZN-c5 food effect Study ZN-c5-006, the ratio of $AUC_{0\text{-}inf}$ after a high-fat meal compared to fasting showed no effect. A small, <20%, decrease in C_{max} was observed when ZN-c5 was administered after a high-fat meal. Although the C_{max} change was statistically significant (lower 90% confidence bound < 0.8), the difference was small compared to the variability of the ZN-c5 exposure in cancer patients and therefore not considered clinically relevant. Based on these results (data on file), ZN-c5 is allowed to be dosed with or without food. This will be implemented only in the Phase 2 parts of the protocol.

4.4 END OF STUDY DEFINITION

The end of the study is defined as when the last patient on study has completed their last study visit (i.e., last safety follow-up or last disease assessment follow-up, whichever is last).

If the primary objectives of the study have been met or the Sponsor decides to stop the study early, the database may be locked for the purpose of analyzing and reporting data. Subjects may continue to receive ZN-c5 per protocol beyond the data cut-off for database lock if the Investigator and the Sponsor agree that the patient's best interests are served by remaining on study treatment.

Limited information including, but not limited to study drug administration, study drug accountability, and non-serious and serious adverse events will be collected in addition to any cases of pregnancy, overdose, or medication error. Less frequent subject visits might be implemented as per institutional standard of care.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Male or female
2) Age ≥ 18 years
3) Menopausal Status [Female subjects]:

   Postmenopausal, as defined by at least one of the following
   a) Age ≥ 60 years;
   b) Age < 60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and FSH level within the laboratory's reference range for postmenopausal females;
   c) Documented bilateral oophorectomy;

   or

   Pre- or peri-menopausal, who must receive a gonadotropin-releasing hormone agonist beginning at least 4 weeks prior to first dose of study medication.
4) Histologically or cytologically confirmed diagnosis of advanced adenocarcinoma of the breast, not amenable to any potential curative intervention
5) Estrogen Receptor (ER) positive disease defined as follows documented by a local laboratory:
   a) [Monotherapy Escalation and Combination Dose Escalation Cohorts]: > 1% positive stained cells based on medical record, archival tumor biopsy, or *de novo* tumor biopsy
   b) [Monotherapy Expansion/Monotherapy Phase 2/Combination Phase 2 Cohorts]: > 10% positive stained cells
6) Human Epidermal Growth Factor Receptor 2 (HER2) negative disease as documented by a local laboratory
   a) [Monotherapy Escalation and Combination Dose Escalation Cohorts]: Documentation by medical record or archival tumor tissue allowed
   b) [Monotherapy Expansion/Monotherapy Phase 2/Combination Phase 2 Cohorts]: Based on analysis of archival tumor biopsy or *de novo* biopsy with HER2-negativity defined as: 1) Immunohistochemistry score 0/1+ or 2) Negative by *in situ* hybridization (FISH/CISH/SISH) defined as a HER2/CEP17 ratio < 2, or for single probe assessment a HER2 copy number < 4
7) [Monotherapy Escalation and Combination Dose Escalation Cohorts]: Refractory to or intolerant of established therapy(ies) known to provide clinical benefit for their malignancy
8) Prior Hormonal Therapy:
   a) [Monotherapy Expansion Cohort]: up to 2 prior lines of endocrine therapy for advanced or metastatic breast cancer
   b) [Monotherapy Phase 2]: 1 or 2 prior lines of endocrine therapy for advanced or metastatic breast cancer
   c) [Combination Phase 2]: up to 1 prior line of endocrine therapy for advanced or metastatic breast cancer

d) Subjects who will undergo a FES-PET must have discontinued all prior ER blocking therapy (e.g., tamoxifen or fulvestrant) for ≥ 60 days before the day of the examination at baseline.

In counting lines of treatment for advanced/metastatic disease, any change in regimen due to PD or toxicity will be counted as a separate line of treatment.

9) Documented prior response to endocrine therapy for advanced or metastatic disease (SD, PR, or CR) lasting > 6 months or disease recurrence after at least 24 months of adjuvant endocrine treatment. (not required for treatment naïve patients)
10) Prior Chemotherapy:
    a) [Monotherapy Dose Escalation Cohort]: Up to 2 prior lines of chemotherapy for the treatment of advanced breast cancer
    b) [Monotherapy Phase 2]: No prior chemotherapeutic regimens for the treatment of advanced breast cancer
    c) [Monotherapy Expansion, Combination Dose Escalation and Combination Phase 2 Cohorts]: Up to 1 prior line of chemotherapy for the treatment of advanced breast cancer

    In counting lines of treatment for advanced/metastatic disease, any change in regimen due to PD or toxicity will be counted as a separate line of treatment.
11) Prior treatment with a CDK4/6 inhibitor is allowed
12) Evaluable or measurable disease per RECIST v1.1.
13) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2
14) All acute toxic effects of any prior anti-tumor therapy resolved to Grade ≤ 1 or baseline (with the exception of alopecia [any grade permitted])
15) Adequate organ function defined as follows:
    a) Hematologic: Platelets ≥ 100×10^9/L; Hemoglobin ≥ 9.0 g/dL; Absolute Neutrophil Count (ANC) ≥ 1.5×10^9/L (without platelet transfusion or any growth factors within previous 7 days of the hematologic laboratory values obtained at Screening visit).
    b) Hepatic: Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 × ULN in case of liver metastases; Total or conjugated bilirubin ≤ 1.5 × ULN.
    c) Renal: Creatinine clearance (CrCl) ≥ 30 mL/min as calculated by the Cockcroft Gault method or serum creatinine ≤ 1.5 × ULN
16) [Premenopausal and perimenopausal female subjects]: Negative serum pregnancy test
17) Male and female subjects of childbearing potential or partners of subjects who engage in intercourse must agree to use protocol specified method(s) of contraception.

5.2 EXCLUSION CRITERIA

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1) Any of the following within the specified window prior to the first dose of study drug:
    a) Tamoxifen, AI, fulvestrant or other anti-cancer endocrine therapy < 14 days
    b) Any chemotherapy < 28 days (or 5 half-lives, whichever is shorter)
    c) Any investigational drug therapy < 28 days or 5 half-lives (whichever is shorter)

d) Prior radiotherapy < 14 days (except for palliative radiotherapy to peripheral sites without residual toxicity)
e) Major surgery < 28 days
f) Minor surgery < 7 days (placement of central venous catheter, fine needle aspiration, or endoscopic biliary stent < 1 day is acceptable)

2) Prior hematopoietic stem cell or bone marrow transplantation
3) Prior radiotherapy to > 25% of bone marrow
4) Brain metastases that require immediate treatment or are clinically or radiologically unstable (i.e., have been stable for < 1 month). If receiving steroids, subjects must be receiving a stable to decreasing corticosteroid dose during at least 1 week before enrollment.
5) Leptomeningeal disease that requires or is anticipated to require immediate treatment.
6) Presence of life-threatening metastatic visceral disease or symptomatic pulmonary lymphangitic spread
7) Other known active cancer(s) likely to require treatment in the next year that would impact the assessment of any study endpoints
8) [Female subjects]: Pregnant or breast-feeding
9) Unexplained symptomatic endometrial disorders (including, but not limited to endometrial hyperplasia, dysfunctional uterine bleeding, or cysts)
10) Uncontrolled symptomatic thyroid dysfunction
11) Impairment of gastrointestinal (GI) absorption for oral medications
12) Nausea, vomiting, or diarrhea > Grade 1
13) Myocardial infarction, symptomatic congestive heart failure (NYHA > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months
14) QTc interval > 480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or history of Torsade de Pointes
15) Concurrent use of food or drugs known to be moderate or strong CYP3A or CYP2C9 inducers and moderate or strong CYP3A4 or CYP2C9 inhibitors. In addition, for moderate or strong CYP3A or CYP2C9 inducers, there should be a wash-out of 14 days (or 5 half-lives, whichever is shorter) before the first administration of study drug (see Section 10.4.6).
16) Any clinically significant disorder, condition, or disease that, in the opinion of the Investigator or Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered on study. A minimal set of information will be collected from these participants to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory

authorities. The information collected will include demography, screen failure details, and eligibility criteria. Subjects may be rescreened after discussion with the Sponsor.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Not applicable.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

6.1.1.1 ZN-c5

ZN-c5 is an oral selective estrogen degrader (SERD) that binds potently to the estrogen receptors alpha and beta (ERα and ERβ). ZN-c5 has not been tested in humans prior to this study. See Investigator's Brochure (IB) for details of ZN-c5.

6.1.1.2 PALBOCICLIB

Palbociclib (IBRANCE®, Pfizer Inc.) is an orally active pyridopyrimidine that is a potent and highly selective reversible inhibitor of Cyclin-Dependent Kinases 4 and 6 (CDK 4/6). The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. There is a strong link between the action of estradiol on the G1-S phase transition, where it drives transcriptional activation of cyclin D1 leading to formation of the cyclin D1-CDK4/6-Rb complex which facilitates the G1 to S phase transition. In nonclinical experiments, palbociclib synergizes with antiestrogen to cause tumor regression in in vitro ER+ advanced breast cancer cell lines. Based on the results of the PALOMA-2 study, palbociclib is approved by the US FDA and other Health Authorities for the treatment of for the treatment of HR+, HER2-negative advanced or metastatic breast cancer in combination with an AI as initial endocrine based therapy in postmenopausal women. Additionally, based on the results of the PALOMA-3 trial which showed a statistically significant improvement in PFS (9.5 months vs 4.6 months for placebo + fulvestrant), palbociclib is approved for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy.

6.1.2 DOSING AND ADMINISTRATION

6.1.2.1 DOSING AND ADMINISTRATION OF ZN-c5

ZN-c5 capsules (25 and 100 mg) will be provided by Zeno Alpha.

Regardless of cohort, subjects should take ZN-c5 once daily at approximately 24-hour intervals (alternatively, this total daily dose may be divided by 2 and administered BID [every 12 hours]).

In the Phase 1 parts of the study, subjects should take ZN-c5 at least 1 hour before or 2 hours after a meal.

In the Phase 2 parts of the study, ZN-c5 can be taken with or without food.

If the subject vomits or misses a dose, an additional dose should not be taken. The subject should wait and take the next dose at the regularly scheduled time. Subjects should not take more than 1 dose of ZN-c5 at a time. Capsules should be swallowed whole (do not chew, crush, or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

6.1.2.2 DOSING AND ADMINISTRATION OF PALBOCICLIB

Palbociclib (IBRANCE®, Pfizer Inc.) at a dose of 125 mg should be taken orally once daily for 21 consecutive days, followed by 7 days off treatment to comprise a complete cycle of 28 days, per the most recent local or US Full Prescribing Information for palbociclib. Subjects should take palbociclib at approximately 24-hour intervals at approximately the same time each day.

On days that PK samples are drawn, palbociclib should be taken with food 2 hours after the ZN-c5 dose.

If a subject vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Palbociclib should be swallowed whole (do not chew, crush, or open them prior to swallowing). Palbociclib should not be ingested if the medication is broken, cracked, or otherwise not intact.

6.1.3 DEFINITION OF MTD AND RP2D

During both the Monotherapy and Combination Dose Escalation cohorts of the study, dose limiting toxicity (DLT) will be assessed during Cycle 1. A cohort will be expanded from 3 to 6 subjects if one of the initial 3 subjects demonstrates DLT. Cohort expansion or dose escalation will follow the rules outlined in Table 2. Subjects who do not receive at least 24/28 doses of ZN-c5 or at least 18/21 doses of palbociclib in Cycle 1 for reasons other than DLT will be replaced.

Table 2: Dose Escalation Rules

If DLT was observed in:	Then:
0 in 3 subjects	Proceed with enrollment in next cohort
1 of 3 subjects	Enroll 3 additional subjects in current cohort
1 of 6 subjects	Proceed with enrollment in next cohort
≥ 2 subjects in a cohort	Do not escalate; enroll 3 additional subjects in previous cohort or new intermediate dose level

The MTD is defined as the highest dose level with ≤ 1 DLT in a cohort of 6 subjects. The RP2D may be lower but will not be higher than the MTD. The MTD/RP2D for monotherapy treatment may be different than the MTD/RP2D for combination therapy.

6.1.4 MONOTHERAPY DOSE ESCALATION

In order to define an MTD or the RP2D for ZN-c5 as a single agent, this study will follow a standard 3+3 design. At least 3 and up to 6 evaluable subjects will be enrolled for each dose cohort. ZN-c5 will be administered orally once daily (alternatively, this total daily dose may be divided by 2 and administered BID [every 12 hours]), on a 28-day cycle (continuous dosing). The total number of patients will depend upon the number of dose escalations necessary, but it is estimated to be approximately 36 subjects.

Dose levels and dosing frequency may be adjusted during the study on the basis of emerging safety and PK data. Intermediate dose levels may be evaluated.

Additional subjects can be enrolled at a lower dose level already deemed well-tolerated; these patients will be part of the Monotherapy Expansion (Section 6.1.6).

At least 6 subjects will be treated at the MTD/RP2D.

The dose levels for the study are shown in Table 3.

Table 3: ZN-c5 Study Dose Levels

Dose Level*	ZN-c5* (once daily)**
1	50 mg
2	75 mg
3	100 mg
4	150 mg
5	300 mg
6	600 mg
7	900 mg
8	1200 mg
*Dose Levels may be modified, and intermittent dose levels may be implemented based on emerging safety and PK results. ** Alternatively, this total daily dose may be divided by 2 and administered BID (every 12 hours).	

6.1.5 COMBINATION DOSE ESCALATION

Dose escalation in combination with palbociclib will be initiated at a ZN-c5 dose that is deemed well-tolerated in the Monotherapy Dose Escalation and will proceed with higher ZN-c5 doses, as tolerated in the Monotherapy Dose Escalation, based on standard rules of 3+3 design in order to define an MTD/RP2D for ZN-c5 in combination with palbociclib (Section 6.1.3). The total number of patients will depend upon the number of dose escalations necessary, but it is estimated to be approximately 40 subjects (including alternate dosing schedules, e.g., BID, and possible backfill).

Dose levels and schedule will follow the dose levels and schedule per the Monotherapy Dose Escalation.

Additional subjects can be enrolled at a lower dose level already deemed tolerated (backfill). At least 6 subjects will be treated at the MTD/RP2D.

The subjects treated in the Combination Dose Escalation can possibly count towards the futility assessment stage accrual (Section 9.2.4, Combination Phase 2).

The dose of palbociclib used in the combination phases of the study will be the Regulatory Authority approved dose and schedule (125 mg PO QD × 21 days, followed by 7 days off treatment).

6.1.6 MONOTHERAPY EXPANSION

To further assess the safety, tolerability, and preliminary efficacy of ZN-c5, the dose expansion with monotherapy will be initiated at a dose selected based on PK, safety and available biomarker data from the Monotherapy Dose Escalation. Expansion at a specific dose level will continue until a higher dose has been deemed well-tolerated (no DLTs in 3 subjects or at most 1 DLT in 6 subjects), at which point expansion accrual will shift to the higher dose level.

Efficacy in the Monotherapy Expansion will be determined by CBR.

The Monotherapy Expansion overall will target balanced accrual between the 3 lines of therapy (1st, 2nd and 3rd hormonal therapy line) across all dose levels.

The total cohort size necessary for futility has been estimated based on futility screening criteria targeting at least 10 evaluable subjects for each line cohort across all dose levels where anti-tumor activity is demonstrated and providing an acceptable false negative risk of concluding that there is no activity if the true CBR is at least 40%. The total number subjects will depend upon the number of dose escalations, but it is not estimated to exceed approximately 45 subjects.

Futility screening

Patients are evaluable for assessment of anti-tumor efficacy (based on CBR) if they were dosed and had at least 1 post-baseline disease/tumor assessment (Section 9.3). CBR as measured using RECIST v.1.1 will be assessed to provide a preliminary, anti-tumor activity evaluation.

6.1.7 MONOTHERAPY PHASE 2

To establish the appropriate dose for further development of ZN-c5, additional subjects will be enrolled to further assess the safety, tolerability, and preliminary efficacy of up to 3 dose levels of single agent ZN-c5 (which can include QD or BID dosing). The ZN-c5 dose levels will be selected based on available safety, PK, anti-tumor activity and biomarker data.

Up to 75 subjects will be enrolled per dose level using a randomized (if 2 or more doses), parallel cohort, non-comparative (estimation) design. Efficacy in the Monotherapy Phase 2 will be determined by CBR and results will be combined with those from subjects with similar treatment characteristics (2^{nd}/3^{rd} Line therapy) and treated at the same dose level of ZN-c5 in the Monotherapy Expansion arm (Section 9.2.3). Therefore, the targeted total N (Phase 2 and same population/dose subjects in the Monotherapy Expansion combined) is 75 subjects per dose level to estimate the CBR rate with certain confidence before proceeding with a larger confirmatory study.

6.1.8 COMBINATION PHASE 2

Following the determination of the MTD/RP2D for ZN-c5 in combination with palbociclib, additional subjects will be enrolled to further assess the safety, tolerability, and preliminary efficacy of ZN-c5 in combination with palbociclib.

ZN-c5 will be administered at the combination RP2D and potentially at a lower dose in combination with palbociclib. The lower ZN-c5 dose will be selected based on available safety, PK and biomarker data.

Efficacy in the Combination Phase 2 will be determined by CBR. The Combination Phase 2 will target balanced accrual between the 2 lines of therapy (1^{st} and 2^{nd} hormonal therapy line) across dose levels.

The Combination Phase 2 portion will follow a randomized, parallel group, non-comparative design, assuming both the RP2D and the lower dose are investigated, or a single dose cohort, if only the RP2D is investigated. Each dose cohort will follow a Simon 2-stage design.

Approximately 56 subjects will be enrolled in each dose cohort. Subjects treated in the Combination Dose Escalation at a demonstrated well-tolerated lower combination dose (no DLTs in 3 subjects or at most 1 DLT in 6 subjects) may also count towards the futility stage accrual, assuming the subjects are evaluable (dosed subjects with at least 1 post baseline disease/tumor assessment [Section 9.3]). The two dose cohorts evaluated in Phase 2 will not use the same subjects from lower dose cohorts in the Phase 1

Combination Dose Escalation phase; for example ZN-c5 50 mg Combination Dose Escalation subjects may count for the 100 mg futility cohort in Phase 2, if that is selected as the lower dose cohort for the Phase 2 component, but will not also count for the RP2D futility cohort, if a higher dose is selected as the RP2D.

Futility (Stage 1) and Efficacy (Stage 2)

Within each dose cohort, 51 evaluable subjects will be enrolled in 2 stages, with 19 subjects in the Futility Stage (Stage 1) and 32 subjects in the Efficacy Stage (Stage 2).

Second stage accrual at each cohort will be completed, assuming that Stage 1 futility criteria are exceeded, with at least 11 subjects with CBR in the first 19 evaluable subjects. An approximate 10% loss for CBR evaluability has been assumed resulting in a total sample size for each dose cohort of approximately 56 subjects or a total sample size of 112 subjects for the Combination Phase 2.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator is responsible for ensuring adequate accountability of all study drug.

Accountability records will be provided to each study site or sites may utilize their own accountability records in order to:

- Record the date received and quantity of study drug kits
- Record the date, subject number, subject initials, the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information
- Study drug should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be reconciled against the Subject Dosing Diaries and recorded in the study drug accountability records. All study drug returned by the subject should be retained for review by the study site monitor prior to destruction.

Unused study drug may be destroyed at the site if the site has the appropriate standard operating procedure (SOP) in place. The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies, as needed. If the site is unable to destroy unused study drug on site, the Sponsor will provide instruction for the return of the study drug for disposal/destruction.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

ZN-c5 will be supplied (and labeled per local regulation) as plain-faced capsules containing 25 mg (white size 4 capsules) or 100 mg (opaque white size 0) of ZN-c5. Please see the Pharmacy Manual for additional details.

Palbociclib (IBRANCE®, Pfizer Inc.) will be supplied (and labeled per local regulation) for the study.

6.2.3 PRODUCT STORAGE AND STABILITY

ZN-c5 capsules should be stored under refrigeration (2°-8°C or 36°-46°F) and protected from light. Storage conditions are specified on the label. The study center will be required to maintain a log of regular temperature readings in the storage area for the duration of the study.

Palbociclib capsules should be stored at controlled room temperature (15–30°C, 59–86°F) in their original container. Please see the most recent local or US Full Prescribing Information for additional information.

Until dispensed to the subjects, all bottles of study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the drug product should not be stored in a container other than the container in which it was supplied. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling ZN-c5 capsules.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

Compliance will be described by dose level in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modification and interruptions).

6.5 CONCOMITANT THERAPY

At Screening, all medications taken up to 30 days prior to the screening visit will be recorded on the eCRF. In addition, supportive therapies given during the course of the study (e.g. blood transfusion, growth factor) should be collected and recorded on the eCRF.

At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable).

6.5.1 PROPHYLACTIC MEDICATIONS AND THERAPY

Premenopausal and perimenopausal women must receive a gonadotropin-releasing hormone agonist starting at least 4 weeks prior to enrollment and repeated, as per the prescribing information of the product administered, for the duration of study treatment.

The use of the following is prohibited during Cycle 1 in dose escalation cohorts:

- Prophylactic hematopoietic growth factors (e.g., G-CSF, erythropoietin)

- Prophylactic blood product transfusions

After Cycle 1, use of these treatments should be dictated by clinical situation and discussed with the Sponsor prior to initiation (when possible).

6.5.2 USE OF CYP3A4 AND CYP2C9 INHIBITORS AND INDUCERS

The following are prohibited at any time during the study:

- Moderate and strong CYP3A4 and CYP2C9 inhibitors

The following are prohibited at any time during the study and for 2 weeks (or 5 half-lives, whichever is shorter) prior to study drug administration:

- Moderate and strong CYP3A4 and CYP2C9 inducers

Examples of moderate and strong CYP3A4 and CYP2C9 inhibitors and inducers are provided in Section 10.4.6.

6.5.3 USE OF OTHER INHIBITORS OR INDUCERS

The following are allowed but should be avoided if possible. If required, doses of these agents may be modified as outlined in the appropriate product insert

- Substrates of CYP2C8 and BCRP
- Substrates of CYP3A

Subjects receiving palbociclib should avoid grapefruit or grapefruit juice. In addition, subject who require coadministration of a strong CYP3A inhibitor may require a reduced dose of palbociclib (see the most recent local or US Full Prescribing Information for palbociclib).

6.5.4 ADDITIONAL PROHIBITED MEDICATIONS

In addition, the following treatments are prohibited during the duration of the time that subjects are on active therapy during the study period:

- Hormone replacement therapy, topical estrogens, megestrol acetate, and selective estrogen receptor modulators
- Drugs known to cause QT interval prolongation (see Section 10.4.1)

6.5.5 RESCUE MEDICINE

Medications required to treat study drug related adverse events may be used as appropriate at the discretion of the investigator. Unless required urgently for patient care, the investigator should discuss such medications with the study monitor prior to use.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from investigational treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol (unless withdrawal of consent by the subject).

Subjects should have an End of Treatment Administration Visit as soon as possible (within 7 days) after the decision is made to discontinue study treatment (Section 7.4).

Subjects will return or will be contacted for a Safety Follow-up Visit 30 days (± 7 days) after the last dose of ZN-c5 taken (Section 7.5).

Subjects without PD at the time of study drug discontinuation will continue to undergo a Disease Assessment Follow-up Visit every 12 weeks (± 7 days) (Section 7.6).

Subjects will be followed for survival and subsequent breast cancer therapies.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM TREATMENT AND FROM THE STUDY

Subjects may be discontinued from the investigational treatment in the following situations:

- Documented progression of disease or clinical progression
- Death
- Investigator discretion
- Non-compliance with study drug or protocol
- Important protocol deviation
- Pregnancy
- Patient discretion
- Withdrawal of consent (subjects are free to withdraw participation at any time)
- Lost to follow-up
- Subjects incorrectly initiated on study treatment
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity
- Liver testing abnormalities meeting Hy's Law criteria (See Section 10.4.7)
- Study termination by the Sponsor

Subjects who are withdrawn from the study but are evaluable will not be replaced. Any subject who is withdrawn and is not evaluable may be replaced to ensure a minimum number of evaluable patients.

Subjects may withdraw from any aspect of the voluntary exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the study.

If there is strong evidence of clinical benefit and reasons to justify continuation of the study drug, even though treatment discontinuation criteria have been met, this decision must be reviewed with the Sponsor, and continuation of therapy may be allowed assuming all other treatment resumption criteria have been met.

Subjects will be discontinued from the study in the following situations:

- Death
- Lost to follow-up
- Withdrawal of consent
- Study end per protocol
- Early study termination by Sponsor

7.3 LOST TO FOLLOW-UP

A participant may be considered lost to follow-up if they fail to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- Attempt to contact the participant and reschedule the missed visit
- Counsel the participant on the importance of maintaining the assigned visit schedule
- Ascertain if the participant wishes to and/or should continue in the study.

Prior to determining that a participant is lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (e.g., at least 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). Contact attempts should be documented in the participant's medical record or study file.

Participants who are unreachable based on the attempts outlined above will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

If study drug is discontinued due to subject decision, the subject may elect to continue with treatment discontinuation assessments, safety follow-up and additional follow-up, if applicable.

7.4 END OF TREATMENT VISIT

At this visit, every effort should be made to perform the procedures listed in the Schedule of Activities for each study phase (Section 1.3).

7.5 SAFETY FOLLOW-UP VISIT

A Safety Follow-up Visit will be conducted 30 ± 7 days after the last administration of ZN-c5. If the subject begins a new anticancer treatment within 30 days of the last administration of study drug, the Safety Follow-up Visit should be performed prior to initiation of the new anticancer treatment, if possible

At this visit, every effort should be made to perform the procedures listed in the Schedule of Activities for each study phase (Section 1.3).

If the subject is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the Safety Follow-up Period.

7.6 DISEASE ASSESSMENT FOLLOW-UP VISITS

Subjects without PD at the time of study drug discontinuation will continue to undergo disease evaluations every 12 weeks ± 7 days until confirmation of PD, initiation of the first subsequent cancer therapy, withdrawal of consent, death, loss to follow-up, or until the study is terminated.

Once a subject has confirmation of PD or has initiated subsequent cancer therapy, whichever occurs first, follow-up will discontinue.

7.7 SURVIVAL FOLLOW-UP VISITS

Once disease progression is confirmed or the first subsequent new breast cancer therapy is initiated, whichever occurs first, the survival follow-up period begins. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (± 14 days) until withdrawal of consent, death, loss to follow up, the end of study (Section 4.4) or the study is terminated earlier by the Sponsor. In addition, all subsequent breast cancer treatments will be recorded.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Section 1.3 and described in the text below. Additional information is provided in the study manual.

8.1.1 COMPUTED TOMOGRAPHY (CT) OR MAGNETIC RESONANCE IMAGING (MRI)

Subjects will be assessed by scans (CT or MRI) or other modalities as appropriate. The same modality of assessment (CT or MRI) and specification (e.g., contrast agent, slice thickness) should be used throughout the study for a given subject.

Imaging will be performed at Screening (within 28 days prior to Cycle 1 Day 1) and every 8 weeks (± 7 days) for 24 weeks. After 24 weeks, scans may be performed every 12 weeks (± 7 days). Additional scans may be performed as clinically indicated to assess tumor progression.

Response assessments will be performed according to the RECIST v1.1 Criteria.

8.2 SAFETY AND OTHER ASSESSMENTS

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Section 1.3 and described in the text below. Additional information is provided in the study manual.

8.2.1 SAFETY ASSESSMENTS

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations, vital signs, and special safety assessments such as ECGs.

8.2.1.1 PHYSICAL EXAMINATION

The Investigator or qualified designee will perform a complete physical examination at Screening and at the End of Treatment visit. Pre-dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from the pre-dose baseline physical examination that represent a clinically significant deterioration will be documented on the AE page of the eCRF.

Weight (without shoes) should be measured with each physical examination.

Height (without shoes) should be measured at Screening only.

Beginning at C1D1, a modified physical examination will be performed to monitor for any changes and will also include weight and assessment of disease-related clinical signs and symptoms.

8.2.1.2 VITAL SIGNS

Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation and temperature. Any abnormal measurements may be repeated and reported as AEs if appropriate.

8.2.1.3 ELECTROCARDIOGRAM (ECG)

Resting, semi recumbent triplicate 12-lead ECGs (reporting ventricular rate, PR interval, QRS complex, QT, and QTc intervals) will be obtained over a 5-minute window at the applicable study visits.

ECGs should be collected prior to PK (or any other blood draw) if collected at the same nominal time point. All efforts should be made to perform the EKG within 10% of the nominal time relative to dosing, however, a protocol deviation applies only if it is missed.

The Investigator or qualified designee will review all ECGs.

8.2.1.4 ECOG PERFORMANCE STATUS

The ECOG Performance Status will be scored using the scale in Section 10.4.3.

8.2.1.5 ADVERSE EVENTS

Subjects will be assessed for adverse events (AEs) per guidelines in the National Cancer Institute (NCI) CTCAE (Version 4.03) at the time points outlined in Section 1.3. Any non-serious AEs reported after initiation of ZN-c5 treatment on Cycle 1 Day 1 and throughout the study will be recorded on the eCRF with appropriate source documentation. The subject will be assessed for AEs until 30 days after the last dose of study drug, but prior to initiation of subsequent breast cancer therapy. Please refer to Section 10.4.4 for CTCAE grading criteria.

Please refer to Section 8.3.5 for additional information on AE reporting.

8.2.1.6 LABORATORY ASSESSMENTS

Screening laboratory samples should be obtained within 7 days prior to Cycle 1 Day 1. Eligibility will be based on local laboratory assessments.

Local laboratory assessments may be collected as required for dose adjustments throughout the study. Local laboratory assessments resulting in a dose change will be reported on the eCRF.

Each site laboratory will be responsible for chemistry, hematology, coagulation, and urinalysis testing per Table 4 and storage of other study samples. Other tests listed in Table 4 will be performed by Sponsor or a designated laboratory. Specific instructions for processing, labeling, and shipping samples will be provided in the appropriate laboratory manual. The date and time of sample collection will be recorded in the subject's source documentation.

Study Day 1 (Cycle 1 Day 1) pre-dose samples may be drawn up to 2 days prior to the visit. Pre-dose samples may be drawn within 1 day of subsequent visits.

Table 4: Analytes

Serum Chemistry	Hematology	Other
Sodium	White Blood Cell (WBC) Count	ZN-c5 concentration
Potassium	Hemoglobin	Concentrations of ZN-c5 metabolite(s) as applicable, may be determined
Chloride	Hematocrit	
Glucose	Platelet Count	
BUN	Neutrophils (ANC)	
Creatinine	Lymphocytes	
Creatinine Clearance[a]	Monocytes	Tumor Biopsy
ALT (SGPT)	Basophils	
AST (SGOT)	Eosinophils	Serum and Plasma for Pharmacodynamic and Exploratory Biomarkers
Alkaline phosphatase[c]	**Coagulation**	
Total bilirubin[b]	PT/INR	
Gamma-GT[c]	aPTT	
Total protein	**Urine**	Plasma 4β-hydroxycholesterol and cholesterol as applicable
Albumin	Urinalysis (visual inspection, microscopic examination, and dipstick test for pH, protein, glucose, WBC, bilirubin, and blood)	
Calcium		
Magnesium		
Phosphate		
Full Lipid Panel[d]		

[a] Cockcroft-Gault using Actual Body Weight: CRCL (mL/min) = [(140-age(years)) × weight(kg) × [0.85 *if Female*]] / (serum creatinine (mg/dL) ×72)

[b] Includes direct bilirubin

[c] If ≥ Grade 3 Alkaline Phosphatase or Gamma-GT, perform a bile acid panel assay (if available locally)

[d] A full lipid panel, regardless of fasting status, will be performed on C1D1, C3D1 (coinciding with the first on-study tumor assessment after 8 weeks) and C7D1 (6 months into the study). This will not be assessed in the Monotherapy Phase 2 part of the study.

8.2.2 PHARMACOKINETIC, PHARMACODYNAMIC, & CORRELATIVE SAMPLES

8.2.2.1 PHARMACOKINETIC SAMPLES

Details of sample preparation and procedures for transfer of samples to the central laboratory are provided in the Laboratory Manual.

Plasma samples for ZN-c5 (and its potential metabolites as applicable) (± palbociclib) will be collected as described in Table 5.

Table 5: Pharmacokinetic Sampling per Study Component

Study Component	N subjects and type of PK	PK Time Points
Monotherapy Dose Escalation	Full ZN-c5 PK in all subjects	Table 6 (Monotherapy)
Monotherapy Expansion – at each dose level assessed	Full ZN-c5 PK in approximately 6 – 12 subjects in total, subjects from the Monotherapy Dose Escalation treated at the same dose level and with evaluable PK data included	Table 6 (Monotherapy)
	Abbreviated ZN-c5 PK schedule for the remaining subjects (optional)	Table 7
Monotherapy Phase 2	Abbreviated ZN-c5 PK schedule in all subjects (optional)	Table 7
Combination Dose Escalation	Full ZN-c5 + palbociclib PK in all subjects	Table 6 (Combination Therapy)
Combination Phase 2 – Stage 1 – at each dose level assessed	Full ZN-c5 + palbociclib PK in approximately 6 – 12 subjects in total, subjects from the Combination Dose Escalation treated at the same dose level and with evaluable PK data included	Table 6 (Combination Therapy)
	Abbreviated ZN-c5 + palbociclib PK schedule for the remaining subjects (optional)	Table 7
Combination Phase 2 – Stage 2	Abbreviated ZN-c5 + palbociclib PK schedule in all subjects (optional)	Table 7

The decision to switch from a full PK schedule to an abbreviated PK schedule (population PK) will depend on the variability of the ZN-c5 PK parameters observed in the subjects with full PK. If required, more subjects in the Monotherapy Phase 2 or in the Combination Phase 2 (Stage 2) will continue to be assessed with full PK.

In the combination cohorts, on PK days, palbociclib should be taken with food 2 hours after the ZN-c5 dose.

Table 6: Full Pharmacokinetic Sampling Time Points

Day on Study	Time (hr)	Monotherapy	Combination Therapy	
		ZN-c5	ZN-c5	Palbociclib
Cycle 1 Day 1 and 15	T=0	**PK** (pre-dose, within 0.5 hrs)	**PK** (pre-dose, within 0.5 hrs)	NA
		Dose *(fasted)*	**Dose** *(fasted)*	NA
	0.5	**PK**	**PK**	NA
	1	**PK**	**PK**	NA
	2	**PK**	**PK** *(prior to Palbociclib dosing)*	**PK** (pre-dose, within 0.5 hrs)
				Dose *(with food)*
	2.5	NA	NA	**PK** (0.5-hr)
	3	NA	NA	**PK** (1-hr)
	4	**PK**	**PK**	**PK** (2-hr)
	6	**PK**	**PK**	**PK** (4-hr)
	8	**PK**	**PK**	**PK** (6-hr)
	10	NA	NA	**PK** (8-hr)
Cycle 1 Day 2 and 16	24	**PK**	**PK**	NA
	26	NA	NA	**PK** (24-hr)
Cycle 1 Day 8		**PK** (pre-dose, within 0.5 hrs)	**PK** (pre-dose, within 0.5 hrs)	**PK**
Cycle 2 Day 1		**PK** (pre-dose, within 0.5 hrs)	**PK** (pre-dose, within 0.5 hrs)	NA
Cycle 3 Day 1		**PK** (pre-dose, within 0.5 hrs)	**PK** (pre-dose, within 0.5 hrs)	NA
Cycle 4 Day 1		**PK** (pre-dose, within 0.5 hrs)	**PK** (pre-dose, within 0.5 hrs)	NA
NA= not applicable				

In case the dosing schedule is changed to BID dosing, an additional PK time point at 12 hours post ZN-c5 dosing will be drawn (optional).

Table 7: Abbreviated Pharmacokinetic Sampling Time Points

Day of Study	Collection Time Points (and Allowable Windows)	ZN-c5	Palbociclib*
Cycle 1 Day 15	Pre-dose (within 0.5 hour prior to ZN-c5 administration)	X	X
	2-hours (± 10 min) post ZN-c5 administration	X	X
	4-hours (± 1 hour) post ZN-c5 administration	X	X
*in the combination parts of the study			

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing, however, samples obtained within 10% of nominal time from dosing are acceptable for up to and including the

12-hour time points. The 24-hour time points should be drawn within ± 1 hour. A protocol deviation only applies if a PK time point is missed.

If the optional On-Treatment tumor biopsy is performed, an additional PK sample should be collected at that time, regardless if tissue was obtained for ZN-c5 tissue concentration.

8.2.2.2 CORRELATIVE (4B-HYDROXYCHOLESTEROL & CHOLESTEROL) SAMPLES

Plasma will be collected (from the same blood draw as for PK) for analysis of 4β-hydroxycholesterol and cholesterol at the following time points of the Monotherapy Dose Escalation and Expansion cohorts:

- [Cycle 1 Day 1] pre-dose (0 hr)
- [Cycle 1 Day 15] pre-dose (0 hr)
- [Cycles 2, 3 and 4 Day 1] pre-dose (0 hour)

No samples will be collected in the Monotherapy Phase 2.

See Lab Manual for sample collection details.

8.2.2.3 ESR1 MUTATION TESTING

A blood sample will be collected for the detection of ESR1 mutations as described in the Schedule of Assessments.

See Lab Manual for sample collection details.

8.2.2.4 BIOMARKER TESTING

Whole blood, plasma and serum biomarkers will be collected at C1D1, C2D1 and at time of disease progression (Section 1.3) and will be used to evaluate the association of exploratory systemic specific biomarkers with study drug response, including efficacy and/or AEs and to increase knowledge and understanding of the biology of breast cancer or related diseases. Biomarker specimens will be collected from all subjects. In addition, sampling time points may be modified during the study based upon emerging data.

For sampling procedures, storage conditions, and shipment instructions, see the Lab Manual.

Remaining plasma samples obtained to measure ZN-c5 levels may also be used to measure the exploratory pharmacodynamic biomarkers.

8.2.2.5 TUMOR BIOPSY TISSUE

Subjects in all portions of the study will have the option to undergo paired biopsies of a lesion. The first biopsy will be obtained after consent and before the first dose of study drug. The second biopsy will be obtained on C2D1 or thereafter. Subjects will also have the option to undergo biopsy of a lesion at the time of disease progression. The biopsy will be used to evaluate for the presence of exploratory biomarker analyses. The Informed Consent Form will address participation in this optional research.

Analyses can include, but are not limited to:

- Estrogen and progesterone receptor expression
- Ki-67
- RNA seq

Biopsies must not be taken from target lesions used to assess anti-tumor efficacy, if possible.

If the optional, On-Treatment tumor biopsy is performed, an additional PK sample should be collected at that time (Section 8.2.2.1). This plasma PK sample should be collected as close as possible, within 2 hours prior to the biopsy. If sufficient tumor material is available, part of the C2D1 tumor biopsy will be used for determination of ZN-c5 tissue concentration (see Section 8.2.2.6).

See Lab Manual for sample collection details.

8.2.2.6 ZN-c5 TUMOR TISSUE CONCENTRATION

A tumor sample from the C2D1 tumor biopsy will be collected to determine ZN-c5 concentrations and concentrations of ZN-c5 metabolite(s), as applicable. The tissue PK sample will be collected unless harvesting of a fresh tumor sample will not leave enough tumor specimen for the immunohistochemistry analyses per Section 8.2.2.5, which have priority.

If tumor tissue is collected for ZN-c5 concentrations, a plasma PK sample should be collected at that time (Section 8.2.2.1).

8.2.2.7 PK AND BIOMARKER SAMPLES FOR OPTIONAL FUTURE RESEARCH

Subjects will be requested to allow the use of any remaining samples to be used for future research.

The Informed Consent Form will contain a separate section that addresses participation in the optional future research. Subjects who decline to participate will check a “no” box in the appropriate section and will not provide a separate signature. Subjects are not required to consent for optional future research in order to participate in this study and have the right to withdraw their consent for optional future research at any time and for any reason. If a subject wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Sponsor.

8.2.2.8 FES-PET

For exploratory purposes, to assess the effect of ZN-c5 on tumor cell proliferation and to measure regional estrogen binding, an optional positron emission tomography (PET) scan with ^{18}F-fluoroestradiol (FES) will be performed as described in the Schedule of Assessments.

Subjects who will undergo this procedure must have discontinued all prior ER blocking therapy (e.g., tamoxifen or fulvestrant) for ≥ 60 days before the day of the examination at baseline.

The detailed endpoints and analytical methods will be specified in the Statistical Analysis Plan (SAP).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before Cycle 1 Day 1 and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of

doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

Clarification of Serious Adverse Events:

- Death is an outcome of an AE, and not an AE in itself
- An SAE may occur even if the subject was not on study drug at the time of occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE
- "In-patient hospitalization" means the subject is formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department
- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms

Given the endpoints of the study, in order to maintain the integrity of the study, the following events that are assessed as unrelated to study drug will not be considered SAEs:

- Progression of underlying disease (breast cancer)
- Death related to progression of underlying disease (breast cancer)

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drug caused or contributed to the disease progression (i.e., by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

Cases of overdose should also be reported on an SAE form within 24 hours of the Investigator becoming aware of the situation (see Section 8.3.8).

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The severity of AEs will be graded using NCI CTCAE, v4.03 (See Section 10.4.4).

For each episode, the highest severity grade attained should be reported.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 8.3.2.

The investigator or qualified sub-investigator is responsible for final review and confirmation of accuracy of event information and assessments.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The investigator or qualified sub-investigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- No: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., 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 (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- No: Evidence exists that the AE has an etiology other than the study procedure.
- Yes: The AE occurred as a result of protocol procedures, (e.g., venipuncture)

8.3.3.3 EXPECTEDNESS

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Assessment of expectedness for SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's Brochure (IB) or relevant local label as applicable.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits, interviews of a study participant presenting for medical care, or upon review by a study monitor.

- The AE Reporting Period begins at the initiation of study medication (C1D1) and ends after the 30-Day Safety Follow-up Visit. All AEs should be followed up until resolution or until the AE is stable, if possible. Sponsor may request that certain AEs be followed beyond the protocol defined follow-up period.
- The SAE Reporting Period begins at the time a study participant signed an Informed Consent Form and ends after the 30-day Safety Follow-up Visit. Investigators are not obligated to actively seek SAEs after the 30-day period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed related to the use of study drug, he/she should promptly document and report the event to the study Sponsor. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be

requested by the study Sponsor or designee (contract research organization [CRO]) and should be provided as soon as possible.

Note: Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study after Cycle 1 Day 1, it will be recorded as an AE.

All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF.

8.3.5 ADVERSE EVENT REPORTING

All AEs (including SAEs) will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately (within 24 hours of identification by the site) report to the Sponsor any SAE, whether or not considered study intervention related, including those listed in the protocol or Investigator's Brochure. The SAE Report must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

To report a Safety Event, please contact the main Safety Management phone/fax/email (or via the applicable country-specific toll-free numbers located in your study binder).

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 SPECIAL SITUATIONS REPORTS

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, and pregnancy reports regardless of an associated AE. Reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure are also considered special situation reports.

- A pregnancy report is used to report any pregnancy in female partners of male subjects on study
- Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer
- Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject
- Misuse is defined as any intentional or inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information
- An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s)
- Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product

All special situation reports must be reported on the special situations report form and forwarded to Sponsor within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug, but do not apply to non-Sponsor concomitant medications. Cases of overdose should also be reported on an SAE form within 24 hours of the Investigator becoming aware of the situation.

Special situations involving non-Sponsor concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Sponsor concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should be appropriately documented as a protocol deviation.

Refer to the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8.3.9 REPORTING OF PREGNANCY

Pregnancies of subjects exposed to ZN-c5 must be reported and relevant information should be submitted to Sponsor using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Sponsor.

To report a pregnancy, please contact the main Safety Management phone/fax/email (or via the applicable country-specific toll-free numbers) located in your study binder.

Refer to Section 10.4.5 for Contraceptive Requirements and Maternal and Paternal Exposure.

8.4 DOSE-LIMITING TOXICITIES AND TOXICITY MANAGEMENT

8.4.1 DEFINITION OF DOSE-LIMITING TOXICITY MONOTHERAPY DOSE ESCALATION

A dose-limiting toxicity (DLT) is a toxicity as defined below, excluding toxicities clearly related to disease progression or intercurrent illness, which occurs during the DLT evaluation period (Cycle 1) in each cohort:

- Grade ≥ 3 hematologic toxicity present for more than 7 days
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)
- Grade 3 thrombocytopenia with bleeding
- Grade ≥ 3 or higher non-hematologic toxicity, except:
    - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
    - Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy
- Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Treatment interruption of ≥ 4 days due to drug-related toxicity
- Liver enzyme and bilirubin abnormalities meeting Hy's Law criteria (See Section 10.4.7)
- Any death not clearly due to the underlying disease or extraneous cause

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and Medical Monitor may take place to determine if this adverse event (AE) should be assessed as a DLT necessitating dose reduction. In addition, any toxicity which occurs during the DLT evaluation period meeting the protocol-defined stopping criteria (Section 7.1) will be considered a DLT.

During the DLT evaluation period (Cycle 1), subjects not completing at least 24 days of scheduled daily dosing of ZN-c5 for reasons other than drug-related toxicity (e.g., withdrawal of consent, rapid disease progression, etc.) may be replaced based on the discretion of the Safety Review Committee.

8.4.2 DEFINITION OF DOSE-LIMITING TOXICITY – COMBINATION DOSE ESCALATION

A DLT is a toxicity as defined below, excluding toxicities clearly related to disease progression or intercurrent illness, which occurs during the DLT evaluation period (Cycle 1) in each cohort:

- Hematologic:
  - Grade 4 neutropenia
  - Febrile neutropenia (defined as neutropenia Grade ≥ 3 [ANC < 1000 cells/mm^3] and a body temperature ≥ 38.5°C) requiring antibiotic or antifungal treatment
  - Any Grade 4 thrombocytopenia (< 25,000/mm^3 or <25.0 x 10^9/L)
- Nonhematologic:
  - Grade ≥ 3 toxicities despite adequate treatment (e.g., nausea, vomiting, diarrhea)
- Other:
  - Any palbociclib treatment delay of greater than 7 days to start Cycle 2

Subjects who do not receive at least 24/28 doses of ZN-c5 and/or at least 85% of palbociclib doses in Cycle 1 for reasons other than DLT will be replaced.

8.4.3 TOXICITY MANAGEMENT

Whether or not considered treatment related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

In the combination cohorts, in cases where a toxicity cannot be clearly attributed to either drug (ZN-c5 or palbociclib), ZN-c5 should be modified or discontinued first.

8.4.3.1 DOSE LEVELS FOR TREATMENT MODIFICATION

ZN-c5

ZN-c5 dose levels for intra-subject treatment modification in the Monotherapy and Combination Dose Escalation will become available as dose levels are being assessed.

ZN-c5 dose levels for treatment modification in the Monotherapy Expansion and Combination Phase 2 are provided in Table 8.

Table 8: ZN-c5 Dose Levels for Treatment Modification in Monotherapy Expansion and Combination Phase 2

Dose Level	Dose of ZN-c5
1	RP2D and schedule from the Monotherapy and Combination Dose Escalation [a]
- 1	-25%, further to be determined based on the Dose Escalation data
- 2	-50%, further to be determined based on the Dose Escalation data

RP2D = recommended Phase 2 dose

[a] Dose Level 1 will be the RP2D or a lower dose from the Monotherapy and Combination Dose Escalation according to the information including the safety, PK, pharmacodynamic and/or preliminary efficacy data.

Subjects who are unable to tolerate ZN-c5 at the lowest dose level should be permanently discontinued from study drug, unless the Investigator considers continuation of treatment at a lower dose to be in the best interest of the subject and the Sponsor's Medical Monitor or designee approves further dose reduction.

Palbociclib

Please follow safety guidelines in the most recent local or US Full Prescribing Information for palbociclib (IBRANCE®, Pfizer Inc.).

8.4.3.2 DOSE ADJUSTMENT OF PALBOCICLIB

For subjects participating in the combination therapy portion of the study with toxicity potentially attributable to palbociclib, please follow safety and toxicity guidelines in the most recent local or US Full Prescribing Information for palbociclib (IBRANCE®, Pfizer Inc.).

Dose holds for reasons other than toxicity (e.g., scheduled surgery) are allowed for up to 21 days. Dose holds for reasons other than toxicity that last more than 21 days require that the subject be removed from study unless deemed in the best interest of the patient to continue and after discussion between the Investigator and the Sponsor's Medical Monitor (Section 7.2).

Unmanageable AEs attributed to palbociclib alone may result in continuation of single agent ZN-c5 therapy as long as none of the treatment discontinuation criteria are met (Section 7.2).

If treatment with ZN-c5 is discontinued, on-study treatment with palbociclib can be continued per protocol unless palbociclib is commercially available and treatment is reimbursed for the patient, then the patient can come off study treatment.

8.4.3.3 DOSE ADJUSTMENT OF ZN-C5

ZN-c5 will be held for any ZN-c5 related Grade ≥ 3 adverse event or any DLT.

ZN-c5 dosing may be restarted if the AE that resulted in the dose hold resolves to ≤ Grade 1 (or baseline) within 21 days. If the toxicity does not resolve to ≤ Grade 1 or baseline within 21 days, ZN-c5 will be permanently discontinued, unless deemed in the best interest of the patient to continue and after discussion between the Investigator and the Sponsor's Medical Monitor (Section 7.2).

Dose holds for reasons other than toxicity (e.g., scheduled surgery) are allowed for up to 21 days. Dose holds for reasons other than toxicity that last more than 21 days require that the subject be removed from study unless deemed in the best interest of the patient to continue and after discussion between the Investigator and the Sponsor's Medical Monitor (Section 7.2).

Doses withheld during a cycle will not be made up. When a dose reduction is required because of AEs/DLTs, no dose re-escalation will be permitted for the duration of study treatment unless mutually agreed upon by the Investigator and Sponsor.

For dose modifications based on the occurrence of ZN-c5 related AEs, see Table 9. Up to 2 dose reductions are allowed.

Table 9: Dose Reduction Criteria ZN-c5: All Phases

Dose Reduction Criteria	Dose Adjustment
Grade 4 (< 0.5 × 10^9/L) neutropenia lasting ≥ 8 days	Reduce 1 dose level or discontinue treatment if occurring at the lowest dose level possible (which is 50 mg/day in the Dose Escalation Cohorts or Dose Level -2 in the Monotherapy Expansion/Phase 2 and Combination Phase 2)[b]
Febrile neutropenia requiring antibiotics	
Grade 4 (< 25 × 10^9/L) thrombocytopenia or Grade 3 (≥ 25 to < 50 × 10^9/L) thrombocytopenia associated with Grade ≥ 3 bleeding and/or requiring platelet transfusions	
Any non-hematologic Grade 3 toxicity[a, c]	
Any non-hematologic Grade 4 toxicity[c]	Discontinue treatment[b]

[a] Grade 3 nausea, vomiting, diarrhea, or constipation for < 48 hours do not require a dose reduction.

[b] If it is in the best interest of the subject to continue treatment in the opinion of the Investigator and after discussion with the Sponsor, the subject can continue treatment at a (further) reduced dose level.

[c] Includes laboratory values deemed clinically significant by the Investigator

If the ZN-c5 dose is reduced, the dose will not be increased again. If a benefit/risk assessment favors the increase of dose up to the initial starting dose after dose reduction, an agreement with the Sponsor's Medical Monitor is required prior to the dose increase.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB/IEC approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB/IEC and the Sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB/IEC project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB/IEC and to the study sponsor within the timelines for SAE reporting outlined in Section 8.3.6.
- Any other UP will be reported to the IRB/IEC and to sponsor within 15 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 15 business days of the IRB/IEC's receipt of the report of the problem from the investigator.

8.5.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

For this study, all statistical analyses will be descriptive. No formal hypothesis testing will be performed.

For the Monotherapy and Combination Dose Escalation, statistical methodology will be applied towards identification of the MTD and for the Monotherapy and Combination Phase 2 setting towards estimation of anti-tumor activity.

Additional details on the planned statistical analyses may be found in the trial SAP.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 MONOTHERAPY DOSE ESCALATION AND COMBINATION DOSE ESCALATION

The primary objective of this part of the study is to identify the MTD, if possible, or the RP2D of ZN-c5 as monotherapy and in combination with palbociclib, and to recommend dose(s) for evaluation in future clinical studies. Hence, the number of patients in the cohorts has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic and pharmacodynamic data while exposing as few patients as possible to the investigational product and procedures.

For the Monotherapy Dose Escalation phase of the study, cohorts of 3-6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary, but it is estimated to be approximately 36 subjects.

The Combination Dose Escalation with palbociclib will be initiated at a dose deemed well-tolerated in the Monotherapy Dose Escalation and proceed with higher ZN-c5 doses, as tolerated, based again on standard rules of a 3+3 design (Section 6.1.4). The total number of patients will depend upon the number of dose escalations necessary, but it is estimated to be approximately 40 subjects (including alternate dosing schedules, e.g., BID, and possible backfill). The subjects in the Combination Dose Escalation might also count towards the futility assessment stage accrual in the Combination Phase 2 (Section 6.1.7, Combination Phase 2).

9.2.2 MONOTHERAPY EXPANSION

The Monotherapy Expansion will be initiated at a dose selected based on PK, safety and any available biomarker data from the ZN-c5 Monotherapy Dose Escalation at a specific dose level will continue until a higher dose has been deemed to be well-tolerated (no DLTs in 3 subjects or at most 1 DLT in 6 subjects in the Monotherapy Dose Escalation), at which point expansion accrual might shift to the higher dose level.

The CBR as measured using RECIST v.1.1 will be assessed to provide preliminary anti-tumor activity evaluation in a patient population thought most likely to respond to ZN-c5.

The Monotherapy Expansion overall will target balanced accrual between the 3 lines of therapy (1st, 2nd and 3rd hormonal therapy line) across dose levels. The total cohort size necessary for futility has been estimated based on futility screening criteria targeting 10 evaluable subjects per line cohort at dose

levels where any anti-tumor activity is demonstrated and providing an acceptable false negative risk of concluding that there is no activity if the true clinical benefit rate is at least 40%.

Subjects are evaluable for the CBR if they have at least 1 post baseline disease/tumor assessment (Section 9.3). CBR as measured using RECIST v.1.1 will be assessed to provide preliminary anti-tumor activity evaluation in a patient population thought most likely to respond to ZN-c5. Data from these cohorts will provide a preliminary assessment of anti-tumor activity based on CBR.

The total number of patients in all expansion cohorts will depend upon the number of dose escalations, but it is not estimated to exceed 45 subjects.

9.2.3 MONOTHERAPY PHASE 2

Up to 3 dose levels with up to 75 subjects per dose level will be enrolled using a randomized (if 2 or more doses), parallel cohort, non-comparative (estimation) design.

Efficacy in the Monotherapy Phase 2 will be assessed as in the Monotherapy Expansion and CBR outcomes in the Monotherapy Phase 2 will be combined with those from subjects in the Monotherapy Expansion arm who were treated with ZN-c5 as 2nd/3rd Line of treatment and dosed at the same ZN-c5 dose in the Monotherapy Expansion. The sample size is determined in order to estimate the CBR at each dose level with certain confidence before proceeding with a larger confirmatory study. Based on the targeted sample size, the precision for a 95% exact confidence interval around a hypothesized 40 – 50% CBR rate is ± 12% at each dose level studied.

Historical estimates for the CBR rate specific to 2nd/3rd Line patients (either post CDK4/6 inhibitor or not) are not readily available. The CBR range was estimated based on two studies, reporting a CBR rate for fulvestrant alone of 40% in 2nd Line or higher (PALOMA-3) and 56% CBR in 1st or 2nd Line (MONARCH-2). The targeted precision will be adequately achieved within the specified range and it will increase further outside of the range, if the true CBR rate is further (higher or lower) from 50%.

9.2.4 COMBINATION PHASE 2

The Combination Phase 2 portion follows a randomized, parallel group, non-comparative design, assuming both the RP2D and the lower dose are investigated, or a single dose cohort, if only the RP2D is investigated. Each dose cohort is independently powered (non-comparative) and follows a Simon 2-stage design.

Approximately 56 subjects will be enrolled in each dose cohort. Subjects treated in the Combination Dose Escalation at lower doses can possibly also count towards the futility stage accrual, assuming the subjects are evaluable. The two dose cohorts evaluated in Phase 2 will not use the same subjects from lower dose cohorts in the Phase 1 Combination Dose Escalation phase; for example, ZN-c5 50 mg Combination Dose Escalation subjects may count for the 100 mg futility cohort in Phase 2, if that is selected as the lower dose cohort for the Phase 2 component but will not also count for the RP2D futility cohort, if a higher dose is selected as the RP2D.

CBR as measured using RECIST v.1.1 will be assessed to provide preliminary anti-tumor activity evaluation in a patient population thought most likely to respond to ZN-c5. Subjects are evaluable for CBR if they have at least 1 post baseline disease/tumor assessment (Section 9.3).

Sample size for each dose cohort is based on a Simon 2-stage design with 80% power at the 1-sided 2.5% alpha level to differentiate between 50% CBR (poor performance) and 70% CBR (promising performance). Fifty-one (51) evaluable subjects will be enrolled in two stages, with 19 subjects in Stage 1 and 32 subjects in Stage 2. The probability of early stopping is 68%. The Combination Phase 2 will target balanced accrual between the 2 lines of prior hormonal therapy (1stand 2nd hormonal therapy line) across dose levels.

Second stage accrual will be completed, assuming that Stage 1 futility criteria are exceeded with at least 11 subjects with CBR in the first 19 evaluable subjects. An approximate 10% loss for CBR evaluability has been assumed resulting in a sample size of approximately 56 subjects for each cohort, resulting in a total sample size of approximately 112 subjects for this trial stage.

9.3 POPULATIONS FOR ANALYSES

Full Analysis Set (FAS)

The FAS includes all subjects who receive ≥ 1 dose of study drug. This analysis set will be used for subject characteristics and efficacy endpoints.

Safety Analysis Set

The Safety Analysis Set for this study will be the same as FAS as this study is not randomized. This analysis set will be used for safety endpoints, study treatment administration and post-study therapy.

DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who take ≥ 24/28 scheduled Cycle 1 doses of ZN-c5 and/or the cumulative dose of palbociclib was ≥ 85% in Cycle 1 (or less, if for reasons due to DLTs) and underwent all treatment and safety procedures through Day 28 or experienced a DLT prior to Day 28. Determination of the MTD will be in the DLT-Evaluable Analysis Set.

Pharmacodynamic and Pharmacokinetic Analysis Sets

The Pharmacodynamic and PK Analysis Sets consist of all subjects in the FAS who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All data will be listed individually by subject. For quantitative parameters, descriptive statistics will include the mean, standard deviation, minimum, median, and maximum. For qualitative parameters, descriptive statistics will include the frequency and percentage. Data collected from this study will be analyzed by a designated biostatistician.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Monotherapy Dose Escalation and Combination Dose Escalation

The primary endpoint is DLTs, as described in Section 8.4.

Monotherapy Expansion

The primary endpoint is safety and tolerability, as described in Section 9.4.4.

Monotherapy and Combination Phase 2

The primary endpoint is CBR, as described in Section 9.4.5.2.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints are the following:

- Safety (Section 9.4.4).
- Efficacy: ORR, DOR, CBR, PFS and OS (Section 9.4.5).
- PK parameters (Section 9.4.10.1)

9.4.4 SAFETY ANALYSES

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized by dose level. Data for the pretreatment will be included in data listings.

9.4.4.1 EXTENT OF EXPOSURE

Descriptive information will be provided by dose level regarding the number of doses of study drug prescribed, the total number of doses taken, the percent of expected doses taken, the number of days of study drug, and the number and timing of prescribed dose modification and interruptions.

9.4.4.2 ADVERSE EVENTS

All AEs will be listed. The focus of AE summary will be on treatment-emergent AEs. A treatment-emergent AE is defined as an AE that occurs or worsens in the period from the first dose of study drug to 30 days after the last dose of study drug.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA https://www.meddra.org/) with descriptions by System Organ Class (SOC), High Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03. The relationship of the AE to the IP will be categorized as related or unrelated.

TEAEs will be summarized by dose level. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent AEs within the same Preferred Term (or SOC) is counted only once for that Preferred Term (or SOC) using the worst severity grade. AE descriptions will be presented

by decreasing frequency for a given SOC and Preferred Term. Separate listings and summaries will be prepared for the following types of treatment-emergent AEs:

- Study drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs

9.4.4.3 LABORATORY EVALUATIONS

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade in the period from the first dose of study drug to 30 days after the last dose of study drug. If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade ≥ 1 in severity) will be considered treatment-emergent.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the local laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc. Hematological and serum biochemistry and their changes from baseline will be summarized by dose level, by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (e.g., during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline to the worst grade post baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

9.4.5 EFFICACY ANALYSES

9.4.5.1 OBJECTIVE RESPONSE RATE

Objective Response Rate is defined as the percentage of subjects with measurable disease who have at least one confirmed response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1).

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

In the case of stable disease, measurements should have met the stable disease criteria for a minimum interval of 8 weeks (8 weeks minus the 7-day visit window) following the start of treatment.

When the investigator is in doubt as to whether progression of disease has occurred and therefore reassesses the subject at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response which occurred after a further anticancer therapy was received will not be included in numerator of the ORR calculation.

The ORR estimates and associated exact 95% CIs using Clopper Pearson methodology will be presented.

9.4.5.2 CLINICAL BENEFIT RATE

The CBR is defined as the percentage of patients who have at least one confirmed response of CR, PR (only if subject has measurable disease), or SD lasting at least for 24 weeks prior to any evidence of progression (as defined by RECIST v1.1).

The CBR estimates and associated exact 95% CIs using Clopper Pearson methodology will be presented.

9.4.5.3 DURATION OF RESPONSE

Duration of Response will be defined as the time from the date of first documented response (that is subsequently confirmed per RECIST v1.1) until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a subject does not progress following a response, then their Duration of Response will use the PFS censoring time.

9.4.5.4 PROGRESSION-FREE SURVIVAL

The PFS is defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST v1.1 or death (by any cause in the absence of progression).

Subjects who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. If the subject has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within two visits of baseline.

If a subject discontinues treatment prior to progression, then these subjects will continue to be followed until evidence of objective disease progression as defined by RECIST v1.1 and their PFS time will be derived as defined above.

If a subject receives a subsequent therapy prior to progression, then these subjects will be censored at the time of the subsequent therapy.

The PFS estimate will be presented using Kaplan-Meier methodology.

9.4.5.5 OVERALL SURVIVAL

The OS is defined as the time from date of first dosing until the date of death. Subjects alive at the time of analysis will be censored at the time of the latest date of survival status assessment.

The OS will be summarized using Kaplan-Meier methodology.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

The baseline value will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

9.4.7 PLANNED INTERIM ANALYSES

An interim futility analysis will be conducted after Stage 1 accrual for each dose cohort in the Combination Phase 2 and necessary minimum follow-up is complete. The guiding futility criteria are presented in Section 9.2, Sample Size Determination.

9.4.8 SUB-GROUP ANALYSES

Subgroups of interest for efficacy and safety analyses will be defined in the SAP.

9.4.9 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual subject data may be listed in tabular form or plotted over time, including Duration of Response, listing of AEs, exposure data, or other endpoint-related data.

9.4.10 EXPLORATORY ANALYSES

Analyses of PK and biomarker parameters are discussed below.

9.4.10.1 PHARMACOKINETIC ANALYSIS

The plasma concentrations of ZN-c5 (and its potential metabolites as applicable) and palbociclib will be summarized for monotherapy and the combination therapy cohorts separately by dose level and nominal sampling time using descriptive statistics. Plasma PK parameters (C_{max}, C_{tau}, AUC_{last}, $t_{1/2}$, and T_{max}, as applicable) will be listed and summarized using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation (%) StD, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± StD, and median (Q1, Q3) if applicable.

9.4.10.2 BIOMARKER ANALYSIS

Descriptive statistics of baseline and change in biomarkers will be provided at each sampling time for all subjects, and by dose.

Exploratory analyses may be performed to evaluate the association of each biomarker or combination of biomarkers with clinical outcomes, and the modulation of biomarkers related to mechanism of action and disease progression.

Exploratory biomarkers analyses that may enhance the understanding of the biological effects, the mechanism of action, or safety, may be performed. Biomarker objectives may be further described and updated based on evolving scientific knowledge of ZN-c5 activity. If an exploratory biomarker analysis is to be performed, a biomarker analysis plan, with details on objectives and analysis methods, will be issued prior to the actual data analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to study participation. The following consent materials are submitted with this protocol:

- Study Participation Informed Consent
- Optional tumor biopsy informed consent
- Optional future research informed consent

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/IEC -approved, and the participant will be asked to read, review, and sign the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

All subjects must sign and date the most recent IRB/IEC-approved Informed Consent Form before any study procedures are performed.

The Informed Consent Form will contain a separate section that addresses participation in the optional future research. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the optional future research. Subjects who decline to participate will check a “no” box in the appropriate section and will not provide a separate signature. Subjects are not required to consent for optional future research in order to participate in this study and have the right to withdraw their consent for optional future research at any time and for any reason. If a subject wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the sponsor.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB/IEC, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or Regulatory Authorities).

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects’ interests.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/IEC, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, Institutional policies, or sponsor requirements.

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, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the sponsor, IRB/IEC, 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. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes and appropriate subject identifiers for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from the study Sponsor, including but not limited to the Investigator's Brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of the 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.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

The biomarker samples will be destroyed no later than 10 years after the end of study unless the subject gives specific consent for the remainder of the samples to be stored for optional future research. If the subject provides consent for optional future research, the samples will be destroyed no later than 10 years after the end of the study.

The specimens consented for optional future research, including body fluids, solid tissues, and derivatives thereof (e.g., RNA, proteins, peptides) will be destroyed no later than 10 years after the end of study. The specimen storage period will be in accordance with the IRB/IEC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

A subject's withdrawal from the study does not, by itself, constitute withdrawal of specimens from the optional genomic research. Likewise, a subject's withdrawal from the optional genomic research does not constitute withdrawal from the study.

In the event of a subject's death or loss of competence, the subject's specimens and data will continue to be used as part of the optional future research.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

The Sponsor is responsible for all aspects of study management and governance. Refer to the study binder for contact information for the Medical Monitor, Clinical Monitor, and other key study personnel and parties.

10.1.5.1 INVESTIGATOR RESPONSIBILITIES

Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice (GCP) Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Sponsor, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Sponsor of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, Informed Consent Form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC on any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

10.1.5.2 SPONSOR RESPONSIBILITIES – PROTOCOL MODIFICATIONS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the study Sponsor. The investigator must submit all protocol modifications to the in accordance with local requirements and receive documented approval before modifications can be implemented.

10.1.6 SAFETY OVERSIGHT

In the Phase 1 Monotherapy and Combination Dose Escalation, the safety and tolerability of each dose level will be assessed by a Safety Review Committee after all subjects in the cohort have been followed for at least 28 days after the first dose of ZN-c5. The Safety Review Committee will consist of the Study Team Physician/Medical monitor (or delegate) who will serve as chair of the committee and the Principal Investigator or delegate from each investigational site (or delegate). Others may be invited on an ad hoc basis, including (but not limited to) project team manager, preclinical team lead, study statistician, or others. Other internal or external experts may be consulted as needed. Frequent safety assessments will be conducted throughout Phase 1 (Monotherapy Expansion) and Phase 2 (Monotherapy and Combination).

10.1.7 CLINICAL MONITORING

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

Representatives of regulatory authorities or of the study Sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency or Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and

applicable regulatory requirements (e.g., Good Laboratory Practices [GLP], Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

The investigator will make available all source documents and other records for this trial to Sponsor's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. Electronic CRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the Electronic Data Capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, that the entries accurately reflect the information in the source documents, and the eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor, contract research organization (CRO) or internal Sponsor staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error). At the conclusion of the trial, Sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 10.1.9.2.

10.1.9.2 STUDY RECORDS RETENTION

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. These documents should be classified

into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Sponsor. The investigator must notify Sponsor before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Sponsor to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

10.1.10 PROTOCOL DEVIATIONS

Refer to the Study Manual for handling of protocol deviations.

10.1.11 PUBLICATION AND DATA SHARING POLICY

A clinical study report will be prepared and provided to the regulatory agency. Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Sponsor in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.
- The investigator will submit to Sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Sponsor's confidential information (see Section 10.1.3).
- The investigator will comply with Sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

Investigators and their study staff may be asked to provide services performed under this protocol, e.g., attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Sponsor will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
AI	Aromatase Inhibitor
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC_{last}	Area Under the Curve Up to the Last Measurable Concentration
BID	Twice daily
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
C1D1	Cycle 1 Day 1
CBR	Clinical Benefit Rate
CDK	Cyclin-Dependent Kinase
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CT	Computed Tomography (scan)
C_{tau}	Trough Concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DILI	Drug-Induced Liver Injury
dL	Deciliter
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of Treatment
ER	Estrogen Receptor
°F	Degrees Fahrenheit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FES	^{18}F-fluoroestradiol
FOB	Functional Observational Battery
FSH	Follicle-Stimulating Hormone
g	Gram

GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
hr	Hour
HNSTD	Highest Non-Severely Toxic Dose
IB	Investigator's Brochure
IC_{50}	Half-maximal Inhibition
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
kg	Kilogram
L	Liter
LD	Longest Diameter
LHRH	Luteinizing Hormone-Releasing Hormone
LTFU	Long-term Follow-up
m	Meter
µg	Microgram
µM	Micromolar
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
min	Minute
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
nM	Nanomolar
NYHA	New York Heart Association
OHRP	Office for Human Research Protections
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression of Disease
PE	Physical Examination
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response

PS	Performance Status
PT	Prothrombin Time
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SERD	Selective Estrogen Degrader
SLD	Sum of the Longest Diameters
SOC	System Organ Class
SOP	Standard Operating Procedure
StD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half Life
TAMR	Tamoxifen-Resistant
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TGI	Tumor Growth Inhibition
T_{max}	Time at which maximum concentration seen
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States

10.4 APPENDICES

10.4.1 LIST OF DRUGS KNOWN TO PREDISPOSE TO TORSADE DE POINTES

Please follow the guidelines for classification per the following website:

https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf

Subjects must not be enrolled if they are taking medications classified as having a Known Risk of Torsade de Pointes (TdP) (KR).

10.4.2 REVISED RECIST GUIDELINES (VERSION 1.1)

Please see reference (E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) European Journal of Cancer 45(2009) 228-247.) for full RECIST guidelines.

Measurable Lesions:

- Tumor ≥ 10 mm in longest diameter (LD) on an axial image on CT or MRI with ≤ 5 mm reconstruction interval If slice thickness > 5 mm, LD must be at least 2 times the thickness
- Tumor ≥ 20 mm LD by chest x-ray (if clearly defined & surrounded by aerated lung); CT is preferred (even without contrast)
- Tumor ≥ 10 mm LD on clinical evaluation (photo) with electronic calipers; skin photos should include ruler Lesions which cannot be accurately measured with calipers should be recorded as non-measurable
- Lymph nodes ≥ 15 mm in short axis on CT (CT slice thickness no more than 5 mm)
- Ultrasound cannot be used to measure lesions

Non-Measurable Lesions:

- All other definite tumor lesions
    - Masses < 10 mm
    - Lymph nodes 10–14 mm in short axis
    - Leptomeningeal disease
    - Ascites, pleural or pericardial effusion
    - Inflammatory breast disease
    - Lymphangitic involvement of skin or lung
    - Abdominal masses or organomegaly identified by physical exam which cannot be measured by reproducible imaging techniques
- Benign findings are NEVER included. Also, do not include equivocal (“cannot exclude”) findings

Target Lesions:

- Choose up to 5 lesions (up to two (2) per organ)
- Add up longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the “sum of the longest diameters” (SLD)

Table 10: Time Point Response: Patients with Target (± Non-target) Disease

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	SD
SD	Non-PD or not all evaluated	No	NE
Not all evaluated	Non-PD	No	PD
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, and NE = unevaluable.

Table 11: Time Point Response: Patients with Non-target Disease Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = unevaluable.

[a] "Non-CR/non-PD' is preferred over "stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 12: Time Point Response: Best Overall Response

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR CR	CR PR	CR SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = unevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij

10.4.3 ECOG PERFORMANCE STATUS

Table 13: ECOG Performance Status

Grade	ECOG Performance Status - Description
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 housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference for ECOG Performance Status: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec; 5(6):649-55

10.4.4 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V4.03

NCI CTCAE v 4.03 can be accessed from the link below:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

10.4.5 CONTRACEPTION AND MATERNAL/PATERNAL EXPOSURE

Contraceptive Requirements for Females

Female subjects of childbearing potential must agree to use protocol specified highly effective method(s) of contraception from the screening visit throughout the study period, 90 days following the last dose of study drug ZN-c5 (and 21 days after the last dose of palbociclib, if applicable) unless the subject chooses continuous heterosexual abstinence as a lifestyle choice. The investigator should counsel subjects on the protocol specified method(s) for avoiding pregnancy during the study. See the listed below for the protocol specified contraceptive methods.

Lactating females must discontinue nursing before study drug administration.

Protocol specified contraceptive methods:

- Complete abstinence from intercourse. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom from the date of Screening until 90 days after last dose of ZN-c5 (and 21 days after the last dose of palbociclib, if applicable):
    - intrauterine device with a failure rate of < 1% per year
    - female barrier method: cervical cap or diaphragm with spermicidal agent
    - tubal sterilization
    - vasectomy in male partner

Female subjects must agree to refrain from egg donation or egg harvesting for the purpose of fertilization during the course of the study for at least 90 days after the last dose of study drug.

Contraceptive Requirements for Males

Male subjects must agree to use condoms and avoid sperm donation from the screening visit throughout the study period, and for at least 90 days after administration of the last dose of study drug.

Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the subject was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 30 days after discontinuing investigational product, then investigators or other site personnel inform appropriate Sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

Paternal exposure

Pregnancy of a subject's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 16 weeks after dosing should be reported to the trial Sponsor on a Pregnancy Report Form and followed up for its outcome.

Guidelines for the EU

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

10.4.6 POTENTIAL DRUG-DRUG INTERACTIONS

Table 14: Examples of CYP3A and CYP2C9 Inhibitors/Inducers

	Moderate	Strong
CYP3A Inhibitor	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
CYP3A Inducer	bosentan, efavirenz, etravirine, modafinil	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
CYP2C9 Inhibitor	amiodarone, felbamate, fluconazole, miconazole, piperine	-
CYP2C9 Inducer	aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir	-

Note: The above lists are not exhaustive. See also:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

10.4.7 HY'S LAW DEFINITION

(Excerpted/adapted from: https://www.fda.gov/media/116737/download)

Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin > 2×ULN, identifies a drug likely to cause severe drug-induced liver injury (DILI) (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. **It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated**. In all cases to date, the small number of Hy's Law cases has arisen on a background of an increased incidence of more modest signs of hepatocellular injury (e.g., greater incidence of 3 **×** ULN elevations in AT than seen in a control group).

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of **3-fold (3 ×) or greater elevations above the upper limit of normal (ULN) of ALT or AST** than the (non-hepatotoxic) control drug or placebo

2. Among trial subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, one or more **also show elevation of serum total bilirubin (TBL) to > 2 × ULN**, without initial findings of cholestasis (elevated serum ALP)

3. **No other reason can be found to explain the combination of increased AT and TBL**, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

10.5 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	9-APR-2018	Added EUDRACT number, removed investigator prompt from title page.	FDA approved protocol entered into Zeno Quality System.
2.0	12-JUL-2018	Clarified, updated, streamlined language throughout the protocol to improve flow and readability	Clarity and readability for the sites.
3.0	25-JUN-2019	Update study design	More efficient study design, optimizing dosing for efficacy and safety considerations, as well as implementing more stringent statistical futility criteria to minimize patients' exposure.
4.0	14-FEB-2020	Update study design	Addition of a Phase 2 Monotherapy part of the study and addition of a cohort with a lower dose of ZN-c5 in the Combination Phase 2 with palbociclib.
5.0	14-SEP-2020	Update study design	Addition of possibility to assess up to 3 dose levels in the Monotherapy Phase 2.
6.0	20-APR-2021	Clarification Phase 2 assessments, food intake and abbreviated PK sampling	Clarifications. In Phase 2, ZN-c5 can be taken with or without food.

11 REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA: Cancer J Clin 2010; 60: 277-300.
2. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365(9472):1687-1717.
3. National Comprehensive Cancer Network. Guidelines for patients: Breast Cancer. http://www.nccn.com/cancer-guidelines.html
4. Prowell TM, Davidson NE. What is the role of ovarian ablation in the management of primary and metastatic breast cancer today? The Oncologist. Breast Cancer. 2004; 9:507-517.
5. Randomized Phase II Study OF Goserelin (G) Plus Fulvestrant (F) vs. G Plus Anastrozole (A) vs. G Alone for HR+, Tamoxifen Pretreated, Premenopausal Woman (ongoing). https://clinicaltrials.gov/ct2/show/NCT01266213
6. Turner NC, Ro J, André F et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med 2015;373:209-19.

12 SPONSOR SIGNATURE PAGE

Study Title:	A Phase 1/2 Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of ZN-c5 Alone and in Combination with Palbociclib in Subjects with Estrogen-Receptor Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breast Cancer
Study Number:	ZN-c5-001
Protocol Version:	6.0
Final Date:	20-APR-2021

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed: PPD **Date:** 25-Apr-2021 | 2:44 PM PDT

PPD MD
PPD Clinical Development
Zeno Alpha, Inc.

13 INVESTIGATOR SIGNATURE PAGE

Study Title:	A Phase 1/2 Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of ZN-c5 Alone and in Combination with Palbociclib in Subjects with Estrogen-Receptor Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breast Cancer
Study Number:	ZN-c5-001
Protocol Version	6.0
Final Date:	20-APR-2021

By signing this protocol, I confirm that I have read and agree to conduct the clinical trial as outlined in the protocol and in compliance with Good Clinical Practice, the Declaration of Helsinki as amended, and all other applicable regulatory requirements. Confidentiality of all information received or developed in connection with this protocol will be maintained by me, as well as all other personnel involved in the clinical trial who are employed by me.

_____ _____

Print Name of Principal Investigator **Signature of Principal Investigator**

_____

Date

14 REVISION HISTORY

Summary of Changes from Previous Version:

Section(s)	Summary of Revisions Made	Rationale
Summary of Changes from Version 5.0 (14 Sep 2020) to Version 6.0 (20 Apr 2021)		
Statement of Compliance	Clarification to include guidance for all countries	Clarification
1.3 Schedule of Activities	The Cycle 1 Day 1, 2, 15, and 16 assessments are adapted/clarified for Phase 2: • No Days 2 and 16 assessments required • ECGs on Days 1 and 15 pre-dose and 2 hours post-dose • Vital signs on Days 1 and 15 pre-dose and 2 hours post-dose • In the combination cohort, on days that palbociclib is to be dosed, it can be taken at the same time as the ZN-c5 dose	Adaptation/clarification of assessments for Phase 2 subjects
4.3 Justification of dose **6.1.2.1 Dosing and administration of ZN-c5**	As of the Phase 2 parts of the study, ZN-c5 can be taken with or without food	Data from Study ZN-c5-006 allow dosing regardless of food
8.2.2.1 Pharmacokinetic Samples	Clarification that in the abbreviated sampling schedule, palbociclib will also be analyzed for subjects in the combination parts of the study	Clarification
Summary of Changes from Version 4.0 (14 Feb 2020) to Version 5.0 (14 Sep 2020)		
Global	The document was edited for readability and consistency including but not limited to administrative changes, correction of typos and errors, and formatting.	Administrative updates and clarifications
Title page, header, Sponsor Signature Page, and Investigator Signature Page	Amendment version and date updated	Administrative
1.3 Schedule of Activities **8.2.2.5 Tumor Biopsy Tissue**	Clarifications of • Acceptance of procedures for Cycle 1 Day 1 • When biopsies and PK sample need to be obtained in respect to dosing of ZN-c5 • On study, serum or urine pregnancy tests are allowed	Procedural clarifications
1.1 Synopsis **6.1.5 Combination Dose Escalation** **9.2.1 Monotherapy Dose Escalation and**	Increase the number of subjects in the combination dose escalation to approximately 40.	The increase is including assessment of alternate dosing schedules, e.g., BID, and possible backfill

Section(s)	Summary of Revisions Made	Rationale
Combination Dose Escalation		
1.1 Synopsis **5.1 Inclusion Criteria**	Clarification that for the Monotherapy Phase 2: 1 or 2 prior lines of endocrine therapy for advanced or metastatic breast cancer are allowed	Clarification
1.1 Synopsis **1.2 Schema** **6.1.7 Monotherapy Phase 2** **9.2.3 Monotherapy Phase 2**	Adapting the Monotherapy Phase 2 design so up to 3 dose levels of ZN-c5 can be assessed.	Gathering more data to declare the RP2D(s) of ZN-c5 as monotherapy with more precision
2.2 Background **6.5.3 Use of other inhibitors or inducers**	Update based on new preclinical data	Update
6.5.1 Prophylactic medications and therapy	Clarification that for pre/perimenopausal women, a gonadotropin-releasing hormone agonist can be repeated on study as per the prescribing information of the product administered.	Clarification
8.2.1.6 Laboratory Assessments	Clarification that the full lipid panel can be done regardless of fasting status	Clarification
10.4.5 Contraception and maternal/paternal exposure	Removal of hormonal contraceptives from the list of protocol-specified contraceptive methods.	Clarification on acceptable protocol-specified contraceptive methods. Hormone-based contraception is excluded because of the mechanism of action of ZN-c5 (SERD).
Summary of Changes from Version 3.0 (25 Jun 2019) to Version 4.0 (14 Feb 2020)		
Global	The document was edited for readability and consistency including but not limited to administrative changes, correction of typos and errors, and formatting.	Administrative updates and clarifications
Global	Revised the description of study from a “dose escalation and expansion” study to “Phase 1/2” study	Clarification
Global	References to “FDA/US” and “Europe” replaced by “Regulatory Authorities”, as appropriate, to reflect the expansion of the study to sites outside of the US and Europe.	To reflect the expansion of study to other regions worldwide, which may be regulated by Health Authorities other than the FDA or European Medicines Agency.
Title page, header, Sponsor Signature Page, and Investigator Signature Page	Amendment version and date updated	Administrative

Section(s)	Summary of Revisions Made	Rationale
Synopsis:	• Description of the study design, study population, objectives, and endpoints were modified for the addition of the Monotherapy Phase 2 component to the study. • Revised the estimated numbers of total subjects and subjects participating in the Phase 2 components of the study • Revised the dosing schedule and design description of the Phase 2 Combination component of the study • Updated the study duration from 36 to 48 months • Increased number of study sites from 30 to 60	Addition of Monotherapy Phase 2 component (to estimate the CBR with certain confidence before proceeding with a larger confirmatory study) and addition of a cohort with a lower dose of ZN-c5 in the Combination Phase 2 component (to assess in parallel both the combination RP2D and a lower dose of ZN-c5 in combination with palbociclib)
Schema	• Figure 1 revised to include the Monotherapy Phase 2 component • Figure 2 revised to reflect design changes to the Phase 2 Combination component	Updates for the addition of the Phase 2 Monotherapy component and the design changes for the Phase 2 Combination component
Schedule of Activities	• Sampling for ZN-c5 pharmacodynamic and exploratory biomarkers at the End-of-Treatment and Disease Follow-up visits were to be collected, as applicable, per the footnote (#13); • Tumor biopsy at End-of-Treatment and Disease Follow-up visits were to be collected, as applicable, per the footnote (#14); • At baseline, if opted in, a fresh tumor biopsy should be obtained (no archival material allowed); • Assessment of ESR1 mutation was changed to always be collected at C2D1 and Disease Follow-up, regardless of status at baseline per the footnote (#16); • Clarified that drug accountability would be assessed from the subject dosing diary (#6); • Clarified that pre-dosing assessments may be performed up to 2 days prior to the Cycle 1, Day 1; and for all subsequent visits, these assessments should be performed within 1 day of the planned visit; • Added text to footnotes clarifying which assessments would not be collected for	Procedural clarifications

Section(s)	Summary of Revisions Made	Rationale
	Monotherapy Phase 2, including non-fasting full lipid panel (#9). • Tumor biopsy: Clarified that subjects had the option to undergo a biopsy of a lesion at the time of disease progression. Also, if sufficient tumor material was available, it was clarified that part of the tumor biopsy at C2D1 was to be used for determination of ZN-c5 tissue concentration. Additionally, if a tumor biopsy was collected at C2D1 or beyond, a plasma PK sample was to be collected (#14). • Clarified the timing of the FES-PET scans (#19)	
Section 2.2	• Changed all reference from KP-868 to ZN-c5 • Added findings from nonclinical toxicology studies • Clarification of findings and interpretation of nonclinical toxicology studies.	• Revisions to ensure consistent reference to the drug product • Safety updates based on completed nonclinical studies
Section 2.3.1	Added safety risks, including potential decrease in erythropoiesis/reticulocytes, sex organ effects, pruritus	Safety updates based on completed nonclinical studies.
Sections 2.3.2, 6.1.1.2	Clarified that palbociclib has been approved by other Regulatory Authorities	Clarification
Section 3	Added Objectives and Endpoints for Phase 2 Monotherapy component	Addition of the Phase 2 Monotherapy Component
Section 4.2	Revised the design description from “Futility screening” to “Screening (estimation)”	Revision of design description
Section 5.1	• Clarified which inclusion criteria are applicable to the Monotherapy Escalation and Monotherapy Phase 2 • Added clarifications on counting prior lines of treatment • Modified the eligible hepatic function upper limit of normal for patients with liver metastases (#15)	• Addition of Phase 2 Monotherapy component • Clarification of prior treatments and eligibility
Section 5.2	• Changed restricted period of prior radiotherapy use from 28 days to 14 days (#1d) • Split Exclusion Criterion defining central nervous system metastases into two criteria with additional details for exclusion (#4 and #5) • Clarified that washout period for moderate or strong CYP3A or CYP2C9 inducers should be 14 days **or 5 half-lives, whichever is shorter**, before first use of study drug (#15).	Clarifications

Section(s)	Summary of Revisions Made	Rationale
Section 5.4	Clarified that subjects may be rescreened after discussion with the Sponsor.	Procedural clarification
Section 6.1.2.2	Deleted "capsules" from palbociclib product description.	Clarification
Section 6.1.3	Clarified that 85% of palbociclib doses was 18/21.	Clarification
Section 6.1.7	Added new section with a description of the Monotherapy Phase 2 component	Addition of Phase 2 Monotherapy Component
Section 6.1.8	• Added description of dose selection and administration of ZN-c5 for the Combination Phase 2 component. • Added design details for the Combination Phase 2 component of the study. • Clarified the number of subjects in each dose cohort and total sample size for the Combination Phase 2. • Clarified which subjects from the Combination Dose Escalation phase can be evaluated in which arm of the Combination Phase 2 component.	Addition of the low ZN-c5 dose to the Phase 2 in combination with palbociclib
Section 6.2.1	Clarified that study drug should be reconciled against the subject dosing diaries for accountability purposes	Clarification
Section 6.2.3	Added that ZN-c5 capsules should also be protected from light during storage.	Procedural clarification
Section 6.5.2	Clarified that washout period for moderate or strong CYP3A or CYP2C9 inducers should be 14 days **or 5 half-lives, whichever is shorter**, before first use of study drug.	Clarification
Section 8.1.1	Clarified that additional modalities of imaging tumors, beyond scans, would be acceptable.	Procedural clarification
Section 8.2.1.5	Clarified that AE assessment should be performed after the last dose of study drug but prior to initiation of subsequent breast cancer therapy.	Procedural clarification
Section 8.2.1.6	• Clarified that pre-dose sampling assessments should be drawn within 1 day of all visits subsequent to Cycle 1 Day 1. • Added clarification that non-fasting full lipid panel would not be assessed in the Monotherapy Phase 2 component of the study in footnote d of Table 4.	Procedural clarification
Section 8.2.2.1	• Added new table (Table 5) that provides a description and reference to the PK sampling schedule (full or abbreviated PK sampling schedule) for each study component. • Added new table (Table 7) that provides a description of the abbreviated PK sampling schedule.	Adapted the PK schedule to full PK and an abbreviated PK schedule as appropriate and added clarifications

Section(s)	Summary of Revisions Made	Rationale
	• Clarified that an additional PK sample should be collected if an optional On-treatment tumor biopsy is performed regardless if tissue was obtained for ZN-c5 tissue concentration.	
Section 8.2.2.5	• Added instruction that part of the C2D1 tumor biopsy is to be used for determination of ZN-c5 tissue concentration if sufficient tumor material is available; • At baseline, if opted in, a fresh tumor biopsy should be obtained (no archival material allowed).	Procedural clarification
Section 8.2.2.6	• Added new section on collection of sample for ZN-c5 tumor tissue concentration. • Clarified that a plasma PK sample should be collected if tumor tissue is collected for ZN-c5 concentrations.	Procedural clarification
Section 8.2.2.8	Deleted specific timepoints for FES assessments and replaced with a reference to the Schedule of Assessments.	Procedural clarification
Sections 8.3.4, 8.3.5, 8.3.6	Re-arranged and clarified the process and timing of reporting AEs and SAEs in these sections.	Procedural clarification
Section 8.3.8	Added instruction for reporting cases of overdose.	Procedural clarification
Section 8.4.3.3, Table 9	Added instruction for dose adjustment instructions for Monotherapy Phase 2 component	Procedural clarification
Section 9.2.3	Added description of the sample size estimates and design of the Monotherapy Phase 2 component of the study.	Addition of Phase 2 Monotherapy Component
Section 9.2.4	Revised and added additional information on the sample size estimate and design of the Combination Phase 2 component of the study.	Addition of the low ZN-c5 dose to the Phase 2 in combination with palbociclib
Section 9.4.2	Added description of the analysis of endpoints in the Phase 2 Monotherapy component of the study.	Addition of Phase 2 Monotherapy Component
Section 10.1.1.1	Clarified that documentation of informed consent is required prior to study participation as opposed to “starting intervention/administering study intervention”.	Procedural clarification
Section 10.1.1.2	Clarified that consent forms must be signed by the participants.	Procedural clarification
Section 10.1.6	Clarified that safety oversight by Safety Review Committee would occur in the Phase 1 Monotherapy and Combination Dose Escalation phases.	Clarification
Section 10.4.1	Replaced list of drugs known to predispose to Torsade de Pointes with an online guideline.	To provide the most up-to-date list and resource guidance for the Investigators