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:	17-Feb-2023

STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Zeno Alpha, Inc.
Protocol Number:	ZN-c5-001
IND Number:	
EUDRACT Number:	2018-001364-27
Investigational Drug:	ZN-c5
Indication:	Advanced Breast Cancer

Protocol 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

Date of First Sign-off (Revision 00): 17Feb2023

STATISTICAL ANALYSIS PLAN SIGN-OFF (REVISION 00)

This document was subject to critical review and has been approved by the Sponsor. ***Refer to the authorized electronic signature and date on the last page.***

Signed by: PPD
Executive Director, Biostatistics & Statistical Programming
Zeno Alpha, Inc.

CHANGE LOG FOR CHANGES MADE AFTER THE INITIAL APPROVAL

Revision Number	Revision Date	Section(s) Modified	Brief Description of Revision(s) or Reason(s) for Revision
Revision 00	17Feb2023	NA	Original document creation

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS	
Abbreviation	**Term**
AE	Adverse Event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-12}	Area under the concentration-time curve from the time of dosing to the end of the dosing interval (12 h post-dose for BID dosing; ZN-c5 only)
AUC_{0-24}	Area under the concentration-time curve from the time of dosing to the end of the dosing interval (24 h post-dose for QD dosing)
AUC_{last}	Area under the plasma concentration-time curve from zero to the time of last quantifiable plasma concentration
AUC_{tau}	Area under the concentration-time curve from the time of dosing to the end of the dosing interval (tau = 12 or 24 hours)
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BUN	Blood urea nitrogen
CBR	Clinical benefit rate
CI	Confidence interval
C_{0-12}	Concentration at the end of the dosing interval (BID dosing; ZN-c5 only)
C_{0-24}	Concentration at the end of the dosing interval QD dosing only
C_{ave}	Average steady-state plasma concentration
CL/F	Apparent total plasma clearance after a single dose oral administration
CL_{ss}/F	Apparent total plasma clearance after multiple dose oral administration
C_{max}	Maximum observed plasma concentration after a single dose administration
$C_{max,ss}$	Maximum observed plasma concentration after multiple dose administration
CPK	Creatine phosphokinase
CR	Complete response

GLOSSARY OF ABBREVIATIONS	
Abbreviation	**Term**
CrCl	Creatinine clearance
C_{trough}	Concentration at the end of the dosing interval (tau = 12 or 24 hours)
CV%	Coefficient of variation
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen Receptor
FAS	Full analysis set
FES	^{18}F-fluoroestradiol
GGT	Gamma-glutamyl-transferase
HER2	Human Epidermal Growth Factor Receptor-2
ICH	International Council for Harmonisation
INR	International normalized ratio
λ_z (Lambda z)	Terminal elimination phase rate constant
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall Survival
PD	Disease progression
PET	Positron emission tomography

GLOSSARY OF ABBREVIATIONS	
Abbreviation	**Term**
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance Status
PT	Prothrombin time
QD	Once daily
QTcB	QT interval adjusted using Bazett's formula
QTcF	QT interval adjusted using Fridericia's formula
RAUC	AUC accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
StD	Standard deviation
$T_{1/2}$	Apparent terminal elimination half life
TEAE	Treatment-emergent adverse events
T_{last}	Time of last observed quantifiable concentration
T_{max}	Time to maximum concentration after a single dose administration
$T_{max,ss}$	Time of maximum observed plasma concentration after multiple dose administration
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution after a single dose oral administration
$V_{z,ss}/F$	Apparent volume of distribution after multiple dose oral administration

GLOSSARY OF ABBREVIATIONS	
Abbreviation	**Term**
WBC	White blood cell

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of ZN-c5-001 Protocol version 6.0 dated 20Apr2021. As with any SAP, the proposed methods and approaches to the data analysis should be deemed as flexible. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, the statistical analysis to a certain degree is iterative since much of the planning is based on assumptions that require verification. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the electronic case report forms (eCRFs). This version of the SAP has been developed using the final version of the protocol mentioned above and the Revision 05 of the annotated eCRFs dated 26Sep2022.

This is a Phase 1/2, open-label, multicenter, dose-escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of ZN-c5 alone and in combination with palbociclib in subjects with estrogen-receptor (ER) positive, human epidermal growth factor receptor-2 (HER2) negative advanced breast cancer (See protocol sections 4.1 to 4.4 for details).

2. STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 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

2.1.2 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

2.2 Secondary Objectives

2.2.1 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 v1.1) as assessed by investigators

2.2.2 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

2.2.3 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
- Characterize the pharmacokinetics (PK) of ZN-c5 (and its potential metabolites as applicable) when given in combination with palbociclib
- Characterize the PK of palbociclib when given in combination with ZN-c5

2.2.4 Monotherapy Expansion Phase 1

- Investigate the preliminary anti-tumor efficacy (CBR) for ZN-c5 as a monotherapy

2.2.5 Monotherapy Dose Escalation and Monotherapy Expansion Phase 1 and Monotherapy Phase 2

- Characterize the PK of ZN-c5 (and its potential metabolites as applicable) when given as oral monotherapy

2.3 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)

3. STUDY DESIGN

3.1 Study 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.). Refer to Figure 1 and Figure 2 for additional details.

This Phase 1/2 study comprises the following parts:

- **Monotherapy Dose Escalation**: In order to define an MTD or the RP2D (defined in protocol section 6.1.3) for ZN-c5 as a single agent, the dose escalation 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 (QD) at sequentially escalating doses starting with 50 mg and potentially up to 1200 mg (alternatively, the total daily dose may be divided by 2 and administered every twelve hours [BID]) (protocol section 6.1.2.1), on a 28-day cycle (continuous dosing). 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.
- **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. Dose levels and schedule will follow the dose levels and schedule per the Monotherapy Dose Escalation. The dose and schedule of palbociclib will be the Regulatory Authority's approved dose and schedule (125 mg orally [PO] QD × 21 days, followed by 7 days off treatment). 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 (Combination Phase 2).
- **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.
- **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. This Monotherapy Phase 2 portion will follow a randomized (if 2 or more doses), parallel cohort, non-comparative (estimation) design and up to 3 dose levels of ZN-c5 will be assessed.
- **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 portion will be determined by CBR. The Combination Phase 2 will target balanced accrual between the 2 lines of therapy (1st and 2nd hormonal therapy line) across dose levels. The Combination Phase 2 portion will follow a randomized, parallel group, non-comparative design, assuming 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.

Dose escalation will be determined by assessing DLTs during Cycle 1 (DLT assessment period). Single agent ZN-c5 and combination regimen dose escalation rules in Phase 1 are described in protocol sections 6.1.3-6.1.5.

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

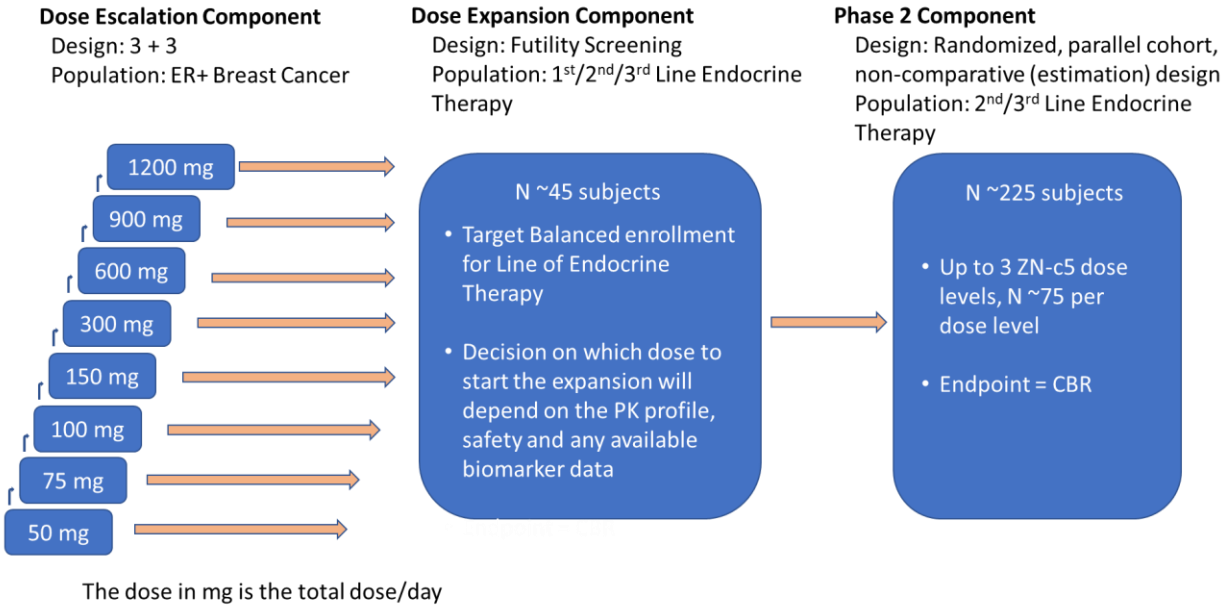
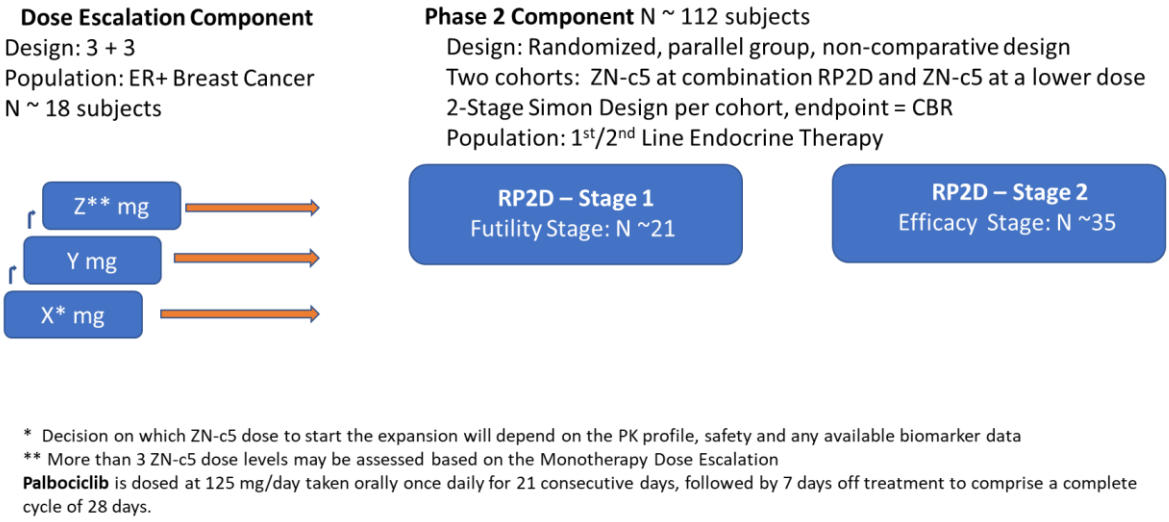


Figure 2 ZN-c5-001 Phase 1 Combination with Palbociclib Dose Escalation and Phase 2



* 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.

3.2 Randomization

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

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. Approximately 56 subjects will be enrolled in each dose cohort. Each dose cohort will follow a Simon 2-stage design.

3.3 Hypothesis Testing

All statistical analyses will be descriptive in nature and no formal hypothesis testing will be performed. Phase 1 statistical methodology will be applied towards identification of the MTD and for Phase 2 towards estimation of anti-tumor activity.

3.4 Interim Analysis

Interim futility analyses will be conducted between stages during the Combination Phase 2. The guiding futility and promising criteria for the combination cohort are presented in Table 1.

Table 1 Sample Size Assumptions and Criteria for Simon's Two-Stage Design

	CBR Assumptions		2-Stage Sample Size	Stage 1 Futility Criteria
	Poor	**Promising**		
ZN-c5 Combination			**1-sided 0.025 alpha level 80% power**	
+ Palbociclib	50%	70%	51 evaluable subjects (approximately 56 total)	≤ 10 of 19 (53%)

3.5 Sample Size

3.5.1 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 subjects in the cohorts has been based on the desire to obtain adequate tolerability, safety and PK and pharmacodynamics data while exposing as few subjects as possible to the investigational product and procedures.

For the Monotherapy Dose Escalation phase of the study, cohorts of 3-6 evaluable subjects will be required. The total number of subjects 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 the standard rules of a 3+3 design (protocol section 6.1.4). The total number of subjects 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 (protocol section 6.1.7, Combination Phase 2).

3.5.2 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 subject 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 (protocol section 9.3). CBR as measured using RECIST v.1.1 will be assessed to provide preliminary anti-tumor activity evaluation in a subject 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 subjects in all expansion cohorts will depend upon the number of dose escalations, but it is not estimated to exceed 45 subjects.

3.5.3 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 subjects (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%.

3.5.4 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 subject 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 (protocol 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 (1st and 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, as outlined in Table 1. 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.

3.6 Study Procedures

All subjects will be assessed by scheduled clinical, laboratory and other diagnostic assessments throughout the study. All efforts should be made to perform assessments as close as possible to the scheduled time points. Visit windows are provided below in Table 2. Study assessments are to be performed as follows:

- Screening evaluations are to be performed within 28 days prior to first study drug dose.
- The day of first administration of study drug will be considered Day 1 of study.
- Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 16 should be conducted on the day of, there is no window allowed. Cycle 1 Day 8 may be conducted ± 1 day, Cycle 1 Day 15 may be conducted ± 2 days.
- Day 1 evaluations for Cycles ≥ 2 may be conducted ± 4 days; Day 15 evaluations for Cycle 2 (only for subjects participating in Combination Therapy) may be conducted ± 2 days. 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.
- Tumor assessments should be performed every 8 weeks (± 7 days) after Cycle 1 Day 1 for the first 24 weeks. After 24 weeks, scans may be performed every 12 weeks (84 days) ± 7 days, and at the time of discontinuation (if not performed within the last 4 weeks ± 7 days).
- End of Treatment assessments should be performed within 7 days from discontinuation of study drug.
- Safety follow-up assessments should be performed 30 days ± 7 days after the last administration of study drug, and prior to the start of new anticancer treatment.
- Disease assessment follow-up assessments should be conducted every 12 weeks (84 days) ± 7 days for subjects without disease progression (PD) at the time of study drug discontinuation until confirmation of PD, initiation of the first subsequent anticancer therapy, withdrawal of consent, death, loss to follow-up or until the study is terminated, whichever occurs first. Survival follow-up should be conducted every 12 weeks (84 days) ± 14 days from the time disease progression is confirmed or the first subsequent new breast cancer therapy is initiated.

3.7 Schedule of Assessments

Table 2 Time and Events Schedule

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]					

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**
Urinalysis[10]	X[7]								X			
Pregnancy Test[11]	X	X					X		X	X		
PK[12]		[X]	[X]	[X]	[X]	[X]	[X]					
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]										

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
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)
Please refer to Section 8 for details on changes on data collection after the specific cut-off date.

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 Protocol 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.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in Everest's Standard Operating Procedures. Detailed data management procedures are documented in the Data Management Plan, Data Validation Check Specifications, and Safety Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

5.1 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.

5.2 Tumor Response Evaluable Set

The Tumor Response Evaluable Set includes all subjects in the FAS with at least 1 evaluable post-baseline response assessment using RECIST 1.1. Subjects who develop PD, intolerable toxicity or death or who discontinue study treatment prior to the first post-baseline assessment will also be considered evaluable and will be classified as non-responders. This analysis set will be used for futility assessment in the Phase 2 combination (if that part is executed) as well as a supportive population in the analysis of efficacy endpoints involving tumor response data. Objective response rate will be assessed in the subset of subjects with measurable disease at baseline.

5.3 Safety Analysis Set

The Safety Analysis Set for this study will be the same as FAS. This analysis set will be used for safety endpoints, study treatment administration and post-study therapy.

5.4 DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who take ≥ 24/28 (≥ 85%) scheduled Cycle 1 doses of ZN-c5 (or less, if for reasons due to DLTs) 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.

5.5 Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set consists of all subjects in the FAS who have the necessary baseline and on-study measurements to provide interpretable results for the pharmacodynamic parameters of interest.

5.6 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set consists of all subjects in the FAS who have on-study measurements to provide interpretable results for the pharmacokinetic parameters of interest and who do not violate the protocol (i.e., not considered an important protocol deviation) in a way that may invalidate or bias the results.

6. STATISTICAL METHODS

6.1 General Data Handling Rules and Definitions

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any enrolled subject is found not having valid documented informed consent, that subject's data will be excluded from the report, except as necessary to document the error.

All analyses will be conducted using SAS version 9.4 or later.

Summary tables for continuous variables will include the following statistics: n (sample size), mean, standard deviation, 95% CIs on the mean (where applicable), median, minimum and maximum. Summary tables for categorical variables will include: n, proportion and 95% CIs on the proportion (where applicable). Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided.

Endpoints will be summarized by relevant study part (escalation, expansion, Phase 2), actual dose level received (on the first day of treatment), therapy (mono or combination), analysis set and time point. As appropriate, changes from Baseline to each subsequent timepoint will be described and summarized. Similarly, as appropriate, the best/worst change from Baseline during the study will also be described and summarized.

The Baseline value will be the last (most recent) pre-treatment value. 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.

Missing data will be maintained as missing unless specified otherwise. For variables where missing data is imputed, the analysis dataset will contain one variable with the imputed value and the original variable with missing maintained as missing.

6.2 Subject Disposition

The number of subjects in each analysis set and the reasons for exclusion will be summarized for all subjects. In addition, the number of subjects who discontinued study treatment and study will also be summarized, along with the reasons for treatment and study discontinuation. Subject eligibility and enrollment details (study phase, cohort, reason subject was not enrolled, assigned dose/frequency) will be listed.

6.3 Protocol Deviations

Important protocol deviations will be summarized by category for all subjects.

6.4 Demographics and Baseline Characteristics

Demographic and Baseline characteristics will be summarized and listed in by-subject listings in the FAS (by dose level in Monotherapy Dose Escalation, by dose cohort in Monotherapy Dose Expansion, Combination Dose Escalation, and Phase 2).

The following demographics, baseline characteristics, medical history and prior cancer treatments will be summarized:

- Demographics variables include age at consent, sex at birth, childbearing potential (for females), race and ethnicity. Age group (18-64, 65-74, 75-84, ≥ 85) will be derived based on age.
- Baseline characteristics include ECOG PS, height and weight, measurable disease (Yes/No, defined as having any target lesion identified at baseline), ESR1 status at baseline (Wild Type, Mutant, Not Assessed) and subcategories (SNV, CNV, Insertion/Deletion) as well as Prior CDK4/6 inhibitor for advanced/metastatic disease (abemaciclib, palbociclib, or ribociclib, Yes/No).
- Medical history includes diagnoses or symptoms entered on the Medical History form. Verbatim descriptions of diagnoses or symptoms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0 or later).
- Cancer history includes stage at initial diagnosis, method of diagnosis, estrogen receptor status and result (%) at diagnosis, progesterone receptor status at diagnosis, HER2 status at diagnosis, HER2 evaluation method at diagnosis, histology, and the most recent tumor stage, estrogen receptor status and result (%), progesterone receptor status, HER2 status and HER2 evaluation method and sites of metastatic disease.
- Time since initial diagnosis in months will be derived, defined as: (date of first treatment – date of initial diagnosis + 1) / 30.4375. For the purposes of calculation, missing day of diagnosis will be imputed as 1; missing month of diagnosis will be imputed as January; no imputation will be made for missing year.
- Prior cancer treatments include radiotherapies entered on the prior cancer therapies form, prior cancer surgeries entered on the surgical history form and prior systemic cancer treatments (intent, regimen, start and end dates, best response, reason for discontinuation, date of relapse/progression on regimen) entered on the prior cancer therapies form.

Prior cancer treatments will be summarized as follows:

- Prior radiotherapy, occurrence (Yes/No) will be summarized categorically for each intent (adjuvant, advanced/metastatic, neoadjuvant, other).
- Prior systemic therapy occurrence (Yes/No) will be summarized categorically for each intent (adjuvant, advanced/metastatic disease, neoadjuvant, other), and number of prior systemic regimens (0, 1, 2, ≥ 3), number of prior systemic regimens for advanced/metastatic disease (0, 1, 2, ≥ 3) including the types of therapy: prior endocrine therapy, prior fulvestrant, prior chemotherapy, prior CDK4/6i, and prior PI3Ki.
- Number of prior systemic regimens for advanced/metastatic disease will be presented ordinally.
- Prior surgical procedure occurrence (Yes/No) will be summarized categorically.

6.5 Efficacy

6.5.1 Study Day and Visit Window Definitions

Study day is defined as the date of assessment – first date of treatment exposure + 1 for assessments that occur on or after the first date of treatment exposure; study day is defined as the date of assessment – first date of treatment exposure for assessments that occur prior to the first date of treatment exposure.

Tumor evaluations prior to first dose are assigned as baseline. Post dosing evaluations/responses during the treatment period will sequentially assigned based on chronology as Tumor Assessment 1, Tumor Assessment 2, etc. including any end of treatment assessments. Assessments collected during follow-up will be similarly assigned based on chronology as Follow-Up Assessment 1, Follow-Up Assessment 2, etc.

6.5.2 Tumor and Response Evaluations

Tumor and response evaluations, PFS and DOR analyses will be based on the FAS and repeated on the Tumor Response Evaluable Set.

Tumor and response evaluations, PFS and duration of response analyses will be based on the FAS and Tumor Response Evaluable Subjects population. Data will be summarized by dose level in Dose Escalation and by cohort in Dose Expansion, and listed in by-subject listings in the Tumor Response Evaluable Subjects population.

Clinical Benefit Rate (CBR) is the primary endpoint for the Monotherapy Phase 2 and Combination Phase 2 and a secondary endpoint for the Monotherapy Escalation Phase 1, Monotherapy Expansion Phase 1, and Combination Escalation Phase 1. It is defined as the proportion of subjects who have at least one confirmed response of CR or PR (only if subject has measurable disease), or SD $\geq$ 24 weeks (or non-CR/non-PD $\geq$ 24 weeks for subjects with non-measurable disease) prior to any evidence of progression. Subjects who develop PD, intolerable toxicity or death or who discontinue study treatment prior to the first post-Baseline assessment will be classified as non-responders.

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 case of SD, measurements should have met the SD criteria for a minimum interval of 8 weeks (8 weeks minus the 7-day visit window) following the start of treatment. Similarly, for non-measurable disease, non-CR/non-PD should be maintained for a minimum interval of 8 weeks (8 weeks minus the 7-day visit window) following the start of treatment.

Best overall response (BOR) will be derived for each subject, based on evaluation of response at each tumor assessment visit per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and reported in the following categories:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
    - SD $\geq$ 24 weeks in duration
    - 8 weeks < SD < 24 weeks in duration
- Non-CR/non-PD
- Progressive Disease (PD)

- Non-Responders (NR)
- Not Evaluable (NE)

Confirmation of PR and CR responses will follow the confirmation process contained in the following table where the best two consecutive time points are considered.

Earlier Best Response (not yet confirmed)	Later Best Response (confirmation)	Best Overall Response
CR	CR	CR
CR	No CR or missing	SD
PR	CR or PR	PR
PR	SD or PD or missing	SD
SD	NA – no confirmation needed	SD
PD	NA	PD

Responses recorded after initiation of anti-tumor therapy are not used (not evaluable) nor are PD responses after a missed visit [>126 days has elapsed since the last image-based response assessment (or first dose date if no prior response)] up to 24 weeks after C1D1. If the previous evaluable image-based response assessment is more than 24 weeks after C1D1, a PD response is considered to be "missed" if more than 26 weeks (182 days) has elapsed. 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 = 49 days) following the start of treatment.

Duration of SD for subjects with best overall response = SD is defined as the time from the day of first study treatment to the start of radiologic disease progression or death. If the subject does not have a radiological disease progression or death, the duration of SD is defined as the time from the day of first study treatment to the date of the last SD assessment. Taking scheduling of imaging into account, a 1 week window will be utilized such that the threshold for 24 weeks will be 23*7 = 161 [response date – first dose date +1 ≥ 161].

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.

Objective Response Rate (ORR) is a secondary endpoint for all cohorts. It 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). Subjects who develop PD, intolerable toxicity or death or who discontinue study treatment prior to the first post-Baseline assessment will be classified as non-responders.

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 change from Baseline and percent change from Baseline will be calculated for each response assessment for the sum of target lesion measurements. The best (minimum) percent change from Baseline will be identified for each subject.

For further details regarding response criteria, refer to protocol Appendix 2 – Tumor Response Criteria.

Best overall response will be summarized categorically based on the four RECIST categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The summary will also include a category for unevaluable (NE) subjects if applicable and one for non-responders (NR). PR and CR must be confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

The clinical benefit rate (CBR) and objective response rate (ORR) estimates will be presented along with the associated Clopper-Pearson 95% CIs.

6.5.2.1 Subgroup Analyses

Subgroup analysis on CBR, ORR and BOR will be performed on FAS as well as Tumor Response Evaluable Set. The following are, but not limited to, potential subgroups for analysis:

- Prior CDK4/6 inhibitor for advanced/metastatic disease (abemaciclib, palbociclib, or ribociclib; Yes, No)
- Baseline ESR1 status (WT, Mutant)

It should be noted that subgroup analyses lead to reduced, often severely reduced, sample sizes in the groups evaluated. This increases the risk for chance findings and interpretation of any results stemming from subgroup analyses should be interpreted with great caution. Only subgroups with adequate cell sizes (i.e. n=5) will be presented in the summaries.

6.5.3 Progression-Free Survival

Progression-free survival (PFS) is a secondary endpoint for all cohorts. It is defined as the time (in months) from the date of first dosing until the date of objective PD (as defined by RECIST version 1.1) or death (by any cause in the absence of progression), whichever occurs earlier: (date of first radiologic PD or death – date of first treatment + 1) / 30.4375.

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 prior to receiving another anticancer therapy. If the subject has no evaluable visits or does not have Baseline data, they will be censored at Day 1 unless situation 3, as described in Table 3, is encountered.

The distribution of PFS will be described in tabular format using Kaplan-Meier methodology[2], reporting estimated median (in months) with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and KM estimated probabilities with corresponding 95% CI is (Kalbfleisch and Prentice 2002) at several time points (including 2, 4, 6, 8, 10 and 12 months).

Refer to Table 3 for censoring rules for PFS.

Table 3 Censoring Rules for Progression-Free Survival

Situation	End Date	Censored
1. Documented radiological PD before initiation of non-study anti-cancer treatment (for subjects with missed tumor assessment, check #3)	Date of the first tumor assessment that determined PD	No
1a*. Clinical PD before initiation of non-study anti-cancer treatment (for subjects with missed tumor assessment, check #3)	Date of Clinical Progression	No
2. Death during the study with no prior PD and no prior initiation of non-study anti-cancer treatment (for subjects with missed tumor assessment, check #3)	Date of death	No
3. Radiologic PD or Death after more than one missed tumor assessment	Date of last adequate tumor assessment prior to missed tumor assessment More than one response assessment is considered to be "missed" if more than 18 weeks (126 days) has elapsed since the last evaluable image-based response assessment (or first dose date if no prior response) up to 24 weeks after C1D1. If the last evaluable image-based response assessment is more than 24 weeks after C1D1, more than one response assessment is considered to be "missed" if more than 26 weeks (182 days) has elapsed. If a subject develops progressive disease or dies after this interval, the tumor response assessment will be excluded from the analysis and censored at the last evaluable assessment.	Yes
4. Non-study anti-cancer treatment initiated before radiologic PD	Date of last adequate tumor assessment prior to initiation of non-study anti-cancer treatment	Yes

Situation	End Date	Censored
5. Subjects still followed without radiologic PD or death as of cutoff date	Date of last adequate tumor assessment (or date of first treatment if no adequate post-Baseline tumor assessments)	Yes
6. Subjects without adequate Baseline tumor assessment	Date of first treatment	Yes

General Considerations:

Radiologic PD for RECIST v1.1 is defined as overall response of 'PD'.

*As a sensitivity analysis, PFS will also be defined using Clinical progression as equivalent to radiological progression. Please refer to situation 1a. The date of clinical progression is defined as the earliest date of any treatment discontinuation for disease progression, in the absence of radiologic PD.

Tumor response assessment dates will be assigned based on the date the image was performed, not the date the image was assessed.

An adequate/evaluable tumor assessment is one with an overall response of CR, PR, SD or PD without prior censoring events (anti-tumor therapy, missed visit).

6.5.3.1 Subgroup Analysis

Subgroup analysis on PFS will be performed on FAS as well as Tumor Response Evaluable Set using the subgroups defined for the CBR subgroup analysis.

6.5.4 Duration of Response

Duration of Response (DOR) is a secondary endpoint for all cohorts. It is defined as the time (in months) from the date of first documented response (that is subsequently confirmed per RECIST version 1.1) until date of documented progression or death in the absence of PD: (date of first radiologic PD or death – date of first response + 1) / 30.4375. The end of response should coincide with the date of progression or death from any cause. The time of initial response will be defined as the latest of the dates contributing to the first visit response of PR or CR.

Subjects who have not progressed following a response at the time of analysis will be censored at the date of last evaluable tumor assessment. Subjects who receive other anticancer therapy prior to documented PD will be censored the day this subsequent therapy started.

DOR will be summarized using Kaplan-Meier methodology[2] in a tabular format.

The proportion of subjects with a DOR of 6 months or more will be summarized.

Censoring rules used for DOR are the same as the ones for PFS (Table 3).

If there are a sufficient number of responses (n=10), DOR will be analyzed using the same methodology as PFS.

6.5.5 Overall Survival

Overall Survival (OS) is a secondary endpoint for all cohorts. It 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.

6.5.6 Pharmacokinetic Variables

Plasma samples for ZN-c5 and its potential metabolites as applicable, and palbociclib (and metabolite) were collected as below. In case the dosing schedule was changed to BID dosing, an additional PK time point at 12 hours post ZN-c5 dosing was drawn (optional).

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				

6.5.7 Pharmacodynamic/Biomarker Analysis

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 PD.

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, this SAP will be updated with details on objectives and analysis methods, prior to the actual data analysis.

6.6 Safety

All safety analyses will be based on the Safety Analysis Set, except for evaluation of DLTs, which will be based on the DLT-Evaluable Analysis Set.

Safety parameters that will be measured in the study are:

- Adverse events
- Dose-limiting toxicities (DLTs; Monotherapy and Combination Therapy Dose Escalations only)
- Laboratory measurements (hematology, coagulation, serum chemistry, urinalysis)
- Vital signs
- ECG
- Physical examination
- ECOG PS

Safety data will be presented descriptively; no formal statistical analyses will be performed.

6.6.1 Study Day and Visit Window Definitions

Nominal visit assignment as collected on the CRF will be used to analyze safety parameters presented by visit. Any unscheduled assessments will not be included in by-visit summaries but are eligible in "worst case" analyses. ECG data collected in triplicate will be averaged and handled as a single collection for visit assignment.

Study day is defined as the date of assessment – first date of exposure + 1 for assessments that occur on or after the first date of exposure; study day is defined as the date of assessment – fist date of exposure for assessments that occur prior to the first date of exposure. The same methodology will be used to define relative cycle day, where day 1 of a given cycle is defined based on the visit date reported on the Date of Visit eCRF.

6.6.2 Extent of Exposure to Study Medication

The following exposure parameters will be calculated separately for each study drug (ZN-c5, and palbociclib, as applicable), with dates of exposure being defined as dates where any study drug is taken.

The **treatment duration** will be calculated as last date of exposure – first date of exposure + 1 for ZN-c5, and last date of exposure – first date of exposure + 8 for palbociclib.

The **number of doses prescribed** will be calculated based on the treatment duration of study drug. For ZN-c5, this will be the number of days of study drug for subjects assigned to QD dosing schedule and will be the number of days of study drug * 2 for subjects assigned to BID dosing schedule. For palbociclib, this will be the ceiling (treatment duration of study drug / 28) * 21.

The **number of doses taken/administered** will be calculated as (treatment duration of study drug * planned number of doses per day) – number of missed doses.

The **percent of expected doses taken/administered** will be calculated as [(number of doses taken/administered) / (number of doses prescribed)] * 100%.

The **total exposure** will be calculated (in mg) for each study drug as the sum of doses taken/administered in mg.

The **actual daily dose** for ZN-c5 and palbociclib will be calculated as the total exposure / number of days of study drug.

The **relative dose intensity (RDI)** for ZN-c5 and palbociclib will be calculated as (actual daily dose / planned daily dose) * 100%.

The **occurrence of dose modifications** (Yes, No) will be derived by subject and reason (AE, other) for each type of modification (drug interruption, dose reduced, dose escalated, drug discontinued).

The **number of dose modifications** will be derived by subject for each type of modification.

6.6.3 Adverse Events

The incidence and severity of adverse events is a primary endpoint in Monotherapy Expansion, along with the incidence and severity of DLTs during Cycle 1 for Monotherapy Dose Escalation and Combination Dose Escalation. The incidence and severity of adverse events is also a secondary endpoint for all cohorts.

Adverse events will be collected and coded using version 25.0 or later of the Medical Dictionary for Regulatory Activities (MedDRA) with descriptions by System Organ Class (SOC), High Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. Analysis of adverse events will be carried out on the Safety Analysis Set.

All AEs will be listed. The focus of AE summary will be on treatment-emergent AEs (TEAE). A TEAE 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.

The severity of AEs will be graded by the Investigator according to the NCI CTCAE, version 4.03. The relationship of the AE to any study drug will be categorized as related or unrelated.

A subject who reports multiple TEAEs within the same Preferred Term (or SOC) is counted only once for that Preferred Term (or SOC) using the worst severity grade.

The TEAEs will be summarized by study part and dose level. Summary tables will be presented to show the number of subjects reporting TEAEs by severity grade and corresponding percentages. 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 TEAEs:

- All TEAEs
- DLTs (Monotherapy Dose Escalation and Combination Dose Escalation) (listing only)

- TEAEs by Grade/Severity
- Study-drug-related TEAEs – for the Phase 1 Combination, these TEAEs will be summarized based on relationship to any study drug, as well separately for ZN-c5 and Palbociclib
- TEAEs that are Grade ≥ 3 in severity
- TEAEs leading to study drug interruption and/or dose modification – for the Phase 1 Combination, these TEAEs will be summarized based on interruption and/or dose modification for any study drug, as well separately for ZN-c5 and Palbociclib
- TEAEs leading to study drug discontinuation – for the Phase 1 Combination, these TEAEs will be summarized based on discontinuation of any study drug, as well separately for ZN-c5 and Palbociclib
- TEAEs with outcome of death (fatal TEAEs)
- Serious TEAEs

Missing Grade:

Missing grades will not be imputed. AEs with missing grade will be reported as 'No Grade'. AEs with missing grade will be counted in "All Grades", but will not be counted in "Grade 3 or higher" columns.

Missing Relationship to Study Drug

An AE with a missing relationship to study drug will be categorized as 'Not determined' and will be included in summaries of related AEs. Imputed values will not be listed in data listings.

Adverse Events with Incomplete Dates

Imputation of dates for adverse events with incomplete dates will be performed only for determination of treatment emergence. Imputed dates will not be presented in data listings. The following algorithm will be used to estimate adverse event start dates for which only partial information is known:

- Missing day and month
    - If the year is same as the year of first day on drug, then the day and month of the start date of drug will be assigned to the missing fields.
    - If the year is prior to the year of first day on drug, then December 31 will be assigned to the missing fields.
    - If the year is after the year of first day on drug, then January 1 will be assigned to the missing fields.
- Missing month only
    - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
    - If the month and year are same as the year and month of first day on drug, then the start date of drug will be assigned to the missing day.

- If the month and year are before the year and month of first day on drug, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of first day on drug, then the first day of the month will be assigned to the missing day.

If the AE stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed using the stop date.

Adverse events with partially missing stop dates will be imputed a stop date as follows:

- Year is missing – date left missing.
- Month is missing:
  - If year = year of data extract, impute as month of data extract;
  - Else, impute 'December'.
- Day is missing:
  - If year and month = year and month of data extract, impute as day of data extract;
  - Else impute 'last day of that month'.

6.6.3.1 Deaths

Summaries of deaths within 30 days of last dose of study medication (including cause of death) as well as a count of those occurring more than 30 days after last dose will be provided. All deaths reported will also be presented in a listing.

6.6.4 Laboratory Data

Laboratory assessments include:

Table 4 Laboratory Tests

Category	Parameters
Hematology	Hemoglobin, hematocrit, platelet count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes)
Coagulation	PT/INR, aPTT
Serum Chemistry	Total protein, albumin, BUN, creatinine, calculated CrCl, total bilirubin with direct bilirubin as applicable, AST (SGOT), ALT (SGPT), alkaline phosphatase, GGT, glucose, sodium, potassium, chloride, calcium, magnesium, phosphate, full lipid panel
Urinalysis	visual inspection, microscopic examination, and dipstick test for pH, protein, glucose, WBC, bilirubin, and blood
Pregnancy Test	β-hCG (for women of childbearing potential) During Screening, a serum pregnancy test must be performed. During the study, urine or serum pregnancy tests can be performed.

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CrCl = creatinine clearance; GGT = gamma-glutamyl-transferase; PT/INR = Prothrombin Time – International Normalized Ratio; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

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.

In addition: Plasma 4β-hydroxycholesterol and cholesterol will be analyzed (from the same blood draw as for PK) 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)

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units; Système International d'Unités).

Hematology, serum chemistry and coagulation tests will be programmatically graded according to NCI-CTCAE v4.03 toxicity grading as detailed in Appendix 1 NCI-CTCAE V4.03 Toxicity Grading 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.

Treatment-emergent laboratory abnormalities will be identified and will be the focus of laboratory data summarization. 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.

For laboratory results entered with inequality symbols (<, ≤, >, ≥), numeric values will be imputed by ignoring the inequality symbol(s) (e.g. "<1.71" will be imputed as 1.71 for numeric analyses). Imputed values will not be listed in data listings.

For each laboratory test, Baseline and worst (maximum) CTCAE grade post-Baseline will be identified for each subject. For parameters for which a CTCAE scale does not exist, the Baseline and worst post-Baseline value will be identified as being below, within or above the normal range as detailed above. Change from Baseline will be calculated for all post-Baseline results.

Subjects will be characterized only once for a given assay, based on the worst severity grade observed during a period of interest (e.g., during the study or from Baseline to a particular visit).

Hematology, coagulation and serum chemistry data, and changes from Baseline will be summarized by dose level, by visit for visits from Baseline to C2D1 as well as EOT. Urinalysis and pregnancy test results will be listed only. Plasma 4β-hydroxycholesterol and cholesterol will be listed only.

Shift tables for hematology, coagulation and serum chemistry will also be presented by showing change in CTCAE severity grade from Baseline to worst grade post-Baseline. A shift table for hematology showing change in CTCAE severity grade from Baseline to worst Cycle 1 value will also be presented.

For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from Baseline to worst post-Baseline category (below, within, or above normal range).

Separate listings and summaries may be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

6.6.5 Vital Signs

Vital signs include height (Baseline only), weight, temperature, pulse rate, respiration rate, systolic blood pressure and diastolic blood pressure, and oxygen saturation. Vital signs and their changes from Baseline will be summarized by visit for visits from Baseline to C2D1 as well as EOT.

6.6.6 Electrocardiogram (ECG)

The electrocardiogram assessment includes PR interval (msec), RR interval (msec), QRS interval (msec), QT interval (msec), QTcB interval (msec), and QTcF interval (msec). Change from Baseline will be calculated for all post-Baseline results. For ECG parameters measured in triplicates, the average of available measures will be computed for each timepoint.

If QTcB is missing and QT and either QTcB or RR is not missing, QTcB will be derived using one of the following formulas:

$$QTcB=QT/(QT/QTcF)^{3/2}$$

$$QTcB=QT/RR^{1/2}$$

The maximum post-Baseline QTcB value will be determined for each subject and categorized (≤ 450, > 450 and ≤ 480, > 480 and ≤ 500, > 500).

The maximum increase from Baseline in QTcB value will be determined for each subject and categorized (≤ 30, > 30 and ≤ 60, > 60).

6.6.7 Physical Examination

The physical examination results will be listed. Clinically relevant abnormalities will be summarized separately as medical history and/or adverse events.

6.6.8 Pregnancy Test

The pregnancy test results will be listed.

6.6.9 Prior and Concomitant Medications/Procedures

Verbatim descriptions of prior and concomitant medications and therapies will be mapped to the World Health Organization Drug Global version Q1 2022 or later.

Verbatim descriptions of concomitant procedures will be coded using version 25.0 or later of the Medical Dictionary for Regulatory Activities (MedDRA) with descriptions by System Organ Class (SOC), High Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term.

A subject who reports multiple medications/procedures within the same Preferred Term (or SOC or ATC code) is counted only once for that Preferred Term (or SOC or ATC code) using the first occurrence chronologically.

Partial medication/procedure dates will be imputed the same way as adverse events dates for the purpose of distinguishing prior and concomitant medications/procedures. Prior medications/procedures are defined as medications/procedures with start date prior to the first dose of study medication. Concomitant medications/procedures are defined as medications/procedures with start date or end date after the first dose of study medication or are ongoing. Medications that start prior to first dose and continue post first dose are considered both prior and concomitant.

Prior and concomitant medications will be summarized separately by Anatomical-Therapeutic-Chemical classification (ATC) class (level 1) and preferred drug name.

Concomitant procedures will be listed. Based on sponsor review, concomitant anti-cancer surgeries and radiotherapy will be flagged in the listing.

6.6.10 ECOG PS

ECOG performance status shifts from Baseline to worst post baseline score will be summarized.

6.7 Pharmacokinetic Analysis

6.7.1 General Considerations

The PK Analysis Set will be used for PK analysis. Any protocol deviations (considered important protocol deviations) that could impact PK parameter estimates will be discussed with the Sponsor to determine whether any data or subject-level exclusions are necessary. All data that are excluded will be listed and the reason for exclusion clearly noted.

If a quantifiable pre-dose concentration of ZN-c5 or palbociclib or metabolites is detected and it represents no more than 5% of the C_{max} value following the first dose of this study, the subject's data will be included in the noncompartmental analysis (NCA), without adjustments. If the observed pre-dose value is greater than 5% of the C_{max} value following the first dose of this study, the subject's data will be excluded from NCA.

Actual sampling time points relative to dosing of each respective drug will be used for NCA, except for the pre-dose time points at Day 1 and Day 15, where the pre-dose time point will be set to 0. If the actual collection time is unknown, the nominal collection time will be used for the purposes of PK parameter estimation.

Concentration values that are below the lower limit of quantification (BQL) will be imputed as follows for NCA:

- BQL values at time points prior to any measurable concentrations for the first dose or at time points immediately prior to dosing for multiple dose will be imputed as 0.
- Any other BQL values will be set to missing.

The above rules should be applied separately for Cycle 1 Day 1 and Day 15 PK parameter estimations.

If there is insufficient amount of sample for the laboratory to report a concentration, then it will be treated as missing.

All PK concentration profiles will be summarized over time by visit, cohort, dosing regimen, and analyte in tabular and graphical formats and pharmacokinetic data will be presented in listings.

All concentration-time data and summary statistics will be reported to the same number of significant figures as displayed in the bioanalytical data, except for percentages, which will be reported to one decimal place.

All PK parameter estimates and summary statistics will be reported to 3 significant figures, with the exception of accumulation ratios (RAUC), metabolic ratios (MR), which will be reported to 3 decimal places, time-related parameters (including T_{last}, T_{max}, and $T_{1/2}$, which will be reported to two decimal places, and AUC_{extr} and CV% which will be reported to 1 decimal place.

6.7.2 Plasma Concentrations

The plasma concentrations of ZN-c5, palbociclib, and/or metabolites will be summarized using nominal sampling time by visit, cohort, dosing regimen (i.e. QD or BID), and analyte using descriptive statistics. A listing by subject of plasma concentrations and/or tumor concentrations of ZN-c5 (if available), sample collection times, and derived sampling time deviations will be provided.

Nominal sampling time points relative to dosing will be used for mean plots of concentration-time data. Actual sampling times will be used for individual concentration-time plots, including all recorded concentrations regardless of timing. BQL concentration values will be set to 0 for predose of Day 1, and set to a value equal to the LLOQ for all other time points for calculation of summary statistics and display. Summary statistics for concentration-time data will include n, mean, SD, arithmetic coefficient of variation (%), minimum, median, maximum, geometric mean, and geometric coefficient of variation (%).

The arithmetic and geometric means of plasma concentrations of ZN-c5, palbociclib, and metabolites, will be presented graphically on both linear and semi-logarithmic scales by visit, cohort, dosing regimen, and analyte. For individual profiles, figures will be presented for each subject with concentration-time profiles on both linear and semi-logarithmic scales. Concentration values of 0 will not be plotted in the semi-logarithmic plots. The following figures will be produced:

- Individual concentration versus actual time – linear scale (overlaid for each cohort)
- Individual concentration versus actual time – semi-log scale (overlaid for each cohort)
- Arithmetic Mean concentration versus nominal time – linear scale (overlaid for all cohorts)
- Arithmetic Mean concentration versus nominal time – semi-log scale (overlaid for all cohorts)
- Geometric Mean concentration versus nominal time – linear scale (overlaid for all cohorts)
- Geometric Mean concentration versus nominal time – semi-log scale (overlaid for all cohorts)

6.7.3 Pharmacokinetic Endpoints

The following PK parameters for ZN-c5, palbociclib, and metabolites will be estimated by NCA using the software Phoenix® WinNonlin® Version 8.3 (Certara, USA).

Table 5 Pharmacokinetic Parameters

PK Parameter	Definition
Cycle 1 Day 1	
Adjusted R^2	Adjusted coefficient of determination
AUC_{0-8}	Area under the plasma concentration time curve from 0 to 8 hours post-dose
AUC_{0-12}	Area under the concentration-time curve from the time of dosing to the end of the dosing interval (12 h post-dose for BID dosing; ZN-c5 only)
AUC_{0-24}	Area under the concentration-time curve from the time of dosing to the end of the dosing interval (24 h post-dose for QD dosing)
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{extr}	The proportion of AUC0-∞ due to extrapolation from time Tlast to infinity, expressed as a %
C_{max}	Maximum observed plasma concentration after a single dose administration
C_{0-12}	Concentration at the end of the dosing interval (BID dosing; ZN-c5 only)
C_{0-24}	Concentration at the end of the dosing interval QD dosing only)
T_{max}	Time of maximum observed plasma concentration after a single dose administration
λ_z	Terminal elimination phase rate constant
$T_{1/2}$	Apparent terminal elimination half life
T_{last}	Time of last observed quantifiable concentration
CL/F^a	Apparent total plasma clearance after a single dose administration
V_z/F^a	Apparent volume of distribution after a single dose oral administration
MR^b	Metabolic ratio of the conversion of a parent drug to its metabolite using AUC_{0-12} or AUC_{0-24} as MR = AUC (metabolite)/AUC (parent), for BID dosing or QD dosing, as appropriate.
Cycle 1 Day 15	
Adjusted R^2	Adjusted coefficient of determination
AUC_{0-8}	Area under the plasma concentration time curve from 0 to 8 hours post-dose
AUC_{tau}	Area under the concentration-time curve from the time of dosing to the end of the dosing interval (tau = 12 or 24 hours)
AUC_{0-24}	Area under the concentration-time curve calculated as 2 × AUC_{0-12} for the BID dose only.
$C_{max,ss}$	Maximum observed plasma concentration after multiple dose administration
$T_{max,ss}$	Time of maximum observed plasma concentration after multiple dose administration
λ_z (Lambda z)	Terminal elimination phase rate constant

PK Parameter	Definition
$T_{1/2}$	Apparent terminal elimination half life
T_{last}	Time of last observable quantifiable concentration
C_{trough}	Concentration at the end of the dosing interval (tau = 12 or 24 hours)
C_{ave}	Average steady-state plasma concentration
CL_{ss}/F[a]	Apparent total plasma clearance after multiple dose oral administration
$V_{z,ss}/F$[a]	Apparent volume of distribution after multiple dose oral administration
MR[b]	Metabolic ratio of the conversion of a parent drug to its metabolite using AUC_{tau} as MR = AUC (metabolite)/AUC (parent), tau = 12 or 24 hours for BID dosing or QD dosing, respectively.
RAUC	AUC accumulation ratio defined as AUC Day 15/AUC Day 1 (where Day 1 AUC_{0-12} or AUC_{0-8} [BID dosing] or AUC_{0-24} [QD Dosing] and Day 15 AUC_{0-8} (BID dosing only) or AUC_{tau}; tau = 12 (BID dosing) or 24 hours)

[a] Determined for parent drug only
[b] Determined for palbociclib and its metabolite

C_{max}, $C_{max\ ss}$, C_{0-12}, C_{0-24}, C_{trough}, T_{max}, and $T_{max,\ ss}$ will be obtained directly from experimental observations. If multiple maxima occur at equal concentrations, the first temporal value will be taken as the $C_{max}/C_{max\ ss}$ and $T_{max}/T_{max,\ ss}$.

$T_{1/2}$, where determinable, will be calculated as the natural logarithm of 2 divided by the terminal phase rate constant, lambda z (λ_z). The number of data points included in the regression will be determined by visual inspection, but a minimum of 3 data points in the terminal phase, excluding $C_{max}/C_{max,ss}$, is required to estimate λ_z. In addition, $T_{1/2}$ should be determined with a span ≥ 2 with span defined as the time interval used to determine lambda_z (i.e., upper lambda_z minus lower lambda_z) divided by the $T_{1/2}$. If this criteria is not met, the $T_{1/2}$ data will be excluded from summary statistics but will listed and flagged.

In order for λ_z-derived parameters (λ_z, V_z/F, V_{ss}/F, and $T_{1/2}$) to be listed and summarized, the adjusted r^2 value reported in Phoenix®WinNonlin® must be ≥ 0.8. In addition, AUC_{extr} must be <20% for Cycle 1 Day 1 PK parameters only (AUC_{inf}). All PK parameters that do not meet these criteria will be listed.

Regression parameters for estimation of λ_z, including the number of time points used, time point range, r-squared, adjusted r-squared, and span will be listed.

For the purpose of calculating AUC, all missing values will be treated as missing in the PK analysis and excluded from analysis except when they occur at pre-dose (of Day 1), where they will be set to 0. Missing pre-dose values for all other days will be handled on a case-by-case basis and may be imputed using the C_{trough} value for that corresponding dosing interval. If Ct_{rough} value is missing, the missing pre-dose will be imputed using the lowest concentration value observed for that corresponding dosing interval, if warranted.

All AUCs including partial AUCs (AUC_{0-8}, AUC_{0-12}, AUC_{0-24}, and AUC_{tau}) will be calculated using the linear trapezoidal method and actual elapsed time values. AUC_{0-24} for the BID dosing will be determined by estimating 2 × AUC_{0-12} for Cycle 1 Day 15. If no PK sample was collected at the 12 or 24 hour post dose for either the BID or QD dosing regimen, one of two approaches will be taken to allow for the determination of AUC_{0-8}, AUC_{0-12}, AUC_{0-24}, or AUC_{tau}:

- For Cycle 1 Day 1, the 12 or 24 hour post-dose sample will be calculated via an extrapolation method using Phoenix® WinNonlin® standard calculations. If no lambda z is estimated, AUC_{0-8}, AUC_{0-12} or AUC_{0-24} will not be estimated. Moreover, the adjusted r^2 value must be ≥ 0.8 and AUC_{extr} must be <20% for AUC_{0-8}, AUC_{0-12}, and AUC_{0-24} to be estimated by extrapolation.
- For Cycle 1 Day 15, the 12 or 24 hour post-dose sample will be imputed using the pre-dose concentration or the minimum observed concentration within that BID or QD dosing interval (if the pre-dose concentration is missing) to obtain the AUC_{tau}.

CL/F on Day 1 will be calculated as Dose (D)/AUC_{0-12} or AUC_{0-24} and CL_{ss}/F on Day 15 will be calculated as Dose (D)/AUC_{tau} (where tau = 12 or 24 hours).

V/F on Day 1 will be calculated as D/(λ*AUC_{0-12} or AUC_{0-24}) and $V_{z,ss}$/F on Day 15 will be calculated as D/(λ*AUC_{tau}) (where tau = 12 or 24 hours).

C_{ave} will be calculated as AUC_{tau}/12 or AUC_{tau}/24 (where tau = 12 or 24 hours).

Plasma PK parameters (see Table 5) will be listed and summarized by cohort, analyte, and visit (Cycle 1 Day 1 or Cycle 1 Day 15) using descriptive statistics for the Safety Analysis Set and PK Analysis Set. Summary statistics for all other PK parameters include n, mean, SD, arithmetic coefficient of variation (%), median, minimum, maximum, geometric mean, and geometric coefficient of variation (%). Summary statistics for the PK parameters T_{max}, $T_{1/2}$, and T_{last} will include n, mean, SD, median, minimum, and maximum.

6.7.4 Pharmacodynamic/Biomarker Analysis

All pharmacodynamic/biomarker data will be presented in listings.

Descriptive statistics of Baseline and change in biomarkers will be provided at each sampling time for all subjects, and by dose/cohort (as applicable).

Longitudinal plots will be presented for selected pharmacodynamic/biomarker parameters.

7. ANALYSES PERFORMED BEFORE DATABASE CLOSURE

Interim futility analyses will be conducted in between stages during the Phase 2 Combination, if applicable. The guiding futility and promising criteria for each cohort are presented in Table 1 and the primary analysis is detailed in Section 6.5.2.

8. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

In regard to the Monotherapy Phase 2 Efficacy, section 6.1.7 of the protocol state that efficacy in the Monotherapy Phase 2 will be determined by CBR and results will be combined with those from subjects with similar treatment characteristics (2nd/3rd Line therapy) and treated at the same dose level of ZN-c5 in the Monotherapy Expansion arm. The analysis will simply be done by phase.

An additional population not defined in the protocol, the Tumor Response Evaluable Set has been defined for use in efficacy analyses.

In a Protocol Clarification Letter (15 June 2022), it was announced that study has reached the time point where a data cut-off of 18 May 2022 has been established after the primary objectives of the study have

been met. Beyond this cut-off, only limited information including study drug administration, study drug accountability, and non-serious and serious adverse events were collected in addition to any cases of pregnancy, overdose, or medication error. End of treatment information (reason for discontinuation form only [EOT], not the full visit) and Safety Follow-up information (Date of Visit [DOV] form only, not the full visit) were also collected.

Because this cut-off was adopted by the sites at different dates, subjects who were ongoing may have data reported beyond this cut-off date.

9. STATISTICAL SOFTWARE

SAS Version 9.4 or later will be used for all statistical analyses.

The PK parameters will be estimated by noncompartmental analysis (NCA) using the software Phoenix® WinNonlin® version 8.1 (Certara, USA).

10. REFERENCES

1. Brookmeyer and Crowley, A Confidence Interval for the Median Survival Time, Biometrics 38, 29-41, March 1982.
2. Kaplan, E. L. Meier, P. (1958). Nonparametric estimation from incomplete observations. J. Amer. Statist. Assn. 53 (282): 457–481. JSTOR 2281868.
3. Klein, J. P. and Moeschberger, M. L. (1997), Survival Analysis: Techniques for Censored and Truncated Data, New York: Springer-Verlag.
4. Kalbfleisch JD, Prentice RL. (2002) The Statistical Analysis of Failure Time Data. Wiley Series in Probability and Statistics.
5. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA guidance, May 2007.
6. Kratz, A, Lewandrowski, K.B. (1998). Normal Reference Laboratory Values. The New England Journal of Medicine, 339, 1063-1072.
7. Kratz, A., Ferraro, M., Sluss, P.M., Lewandrowski, K.B. (2004). Normal Reference Laboratory Values. The New England Journal of Medicine, 351, 1548-1563.
8. PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group. (2014). Analyses and Displays Associated to Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials [White paper]. Retrieved April 9, 2019 from: https://www.phuse.eu/documents/working-groups/deliverables/analyses-displays-associated-to-non-compartmental-pharmacokinetics-version-10-25-mar-14-pdf-11803.pdf
9. Guideline, ICH Harmonised Tripartite. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs E14. 2005.

11. APPENDIX 1 NCI-CTCAE V4.03 TOXICITY GRADING

11.1 Panel: Chemistry

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin, serum- low (hypoalbuminemia)	g/L	[30, LLN)	[20, 30)	<20	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase (ALK) increased	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 20*ULN]	>20*ULN
Alanine aminotransferase (ALT) increased	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Aspartate aminotransferase (AST) increased	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Bilirubin increased	µmol/L	(ULN, 1.5*ULN]	(1.5*ULN, 3*ULN]	(3*ULN, 10*ULN]	>10*ULN
Calcium high (hypercalcemia)	mmol/L	(ULN, 2.9]	(2.9, 3.1]	(3.1, 3.4]; hospitalization indicated	>3.4; life-threatening consequences
Calcium low (hypocalcemia)	mmol/L	[2.0, LLN)	[1.75, 2.0)	[1.5, 1.75); hospitalization indicated	[0, 1.5); life threatening consequences
Creatine phosphokinase (CPK) increased	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 10*ULN]	>10*ULN
Creatinine increased	µmol/L	(1 – 1.5*baseline]; (ULN, 1.5*ULN]	(1.5 – 3.0* baseline]; (1.5*ULN, 3*ULN]	>3.0*baseline; (3*ULN, 6*ULN]	>6*ULN
Gamma-glutamyl-transferase	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 20*ULN]	>20*ULN
Glucose high (hyperglycemia)	mmol/L	(ULN, 8.9]	(8.9, 13.9]	(13.9, 27.8]; hospitalization indicated	>27.8; life threatening consequences
Glucose low (hypoglycemia)	mmol/L	[3.0, LLN)	[2.2, 3.0)	[1.7, 2.2)	[0, 1.7); life threatening consequences; seizures

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Magnesium low (hypomagnesemia)	mmol/L	[0.5, LLN)	[0.4, 0.5)	[0.3, 0.4)	<0.3; life-threatening consequences
Magnesium high (hypermagnesemia)	mmol/L	(ULN, 1.23]	undefined	(1.23, 3.3]	>3.3; life-threatening consequences
Phosphates (hypophosphatemia)	mmol/L	[0.8, LLN)	[0.6, 0.8)	[0.3, 0.6)	[0, 0.3); life threatening consequences; seizures
Potassium high (hyperkalemia)	mmol/L	(ULN, 5.5]	(5.5, 6]	(6, 7]; hospitalization indicated	>7; life-threatening consequences
Potassium low (hypokalemia)	mmol/L	[3, LLN)	[3, LLN); symptomatic; intervention indicated	[2.5, 3); hospitalization indicated	[0, 2.5); life-threatening consequences
Sodium high (hypernatremia)	mmol/L	(ULN, 150]	(150, 155]	(155, 160]; hospitalization indicated	>160; life-threatening consequences
Sodium low (hyponatremia)	mmol/L	[130, LLN)	undefined	[120, 130)	[0, 120); life-threatening consequences

11.2 Panel: Hematology

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin increased	g/dL	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	undefined
Hemoglobin decreased	g/L	[100, LLN)	[80, 100)	[0, 80); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	10^9/L	[75, LLN)	[50, 75)	[25, 50)	[0, 25)
WBC increased	10^9/L	undefined	undefined	>100	undefined
WBC decreased	10^9/L	[3, LLN)	[2, 3)	[1, 2)	[0, 1)
Lymphocytes increased	10^9/L	undefined	(4, 20]	>20	undefined
Lymphocytes decreased	10^9/L	[0.8, LLN)	[0.5, 0.8)	[0.2, 0.5)	[0, 0.2)

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	10^9/L	[1.5, LLN)	[1, 1.5)	[0.5, 1)	[0, 0.5)

11.3 Panel: Coagulation

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
International normalized ratio of prothrombin time (INR) increased	NA	(ULN, 1.5xULN]	(1.5xULN, 2xULN]	>2xULN	-
Activated partial thromboplastin time prolonged	Seconds	(ULN, 1.5xULN]	(1.5xULN, 2.5xULN]	>2.5 x ULN	-

11.4 Panel: Lipid Panel

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Cholesterol high	mmol/L	(ULN, 7.75]	(7.75, 10.34]	(10.34, 12.92]	>12.92
Triglycerides high (hypertriglyceridemia)	mmol/L	(1.71, 3.42]	(3.42, 5.7]	(5.7, 11.4]	>11.4

* Conditions will not be checked programmatically.

Reference: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06 14_QuickReference_5x7.pdf

12. APPENDIX 2 PROGRAMMING CODES FOR STATISTICAL ANALYSIS

Programming of the tables, listings and figures will be performed using SAS Version 9.4 or later, running under UNIX environment. The following table presents the SAS codes for the analyses of response endpoints.

Endpoint	Test	SAS Code

ORR, CBR	Clopper-Pearson (exact) 95% confidence interval	ods listing close;
		proc freq data = indata;
		ods output BinomialCLs=CI BinomialProp=prop;
		table objresp / binomial(level = 1 exact) out=freq1 (keep=objresp count);
		run;
		ods listing;

PFS, DOR, OS	Kaplan-Meier: median, 95% CI, 25th-75th percentile	ods listing close;
		ods output Quartiles=Quartile;
		proc lifetest data=indata;
		time timevar*censvar(1);
		run;
		ods output close;
		ods listing;

Signature Page for VV-CLIN-000247 v1.0

eSignature Approval Task	PPD Clinical 21-Feb-2023 16:30:29 GMT+0000

Signature Page for VV-CLIN-000247 v1.0