Document Type	Clinical Study Protocol
Official Protocol Title	A Phase 2b Study of ZEN003694 in Combination With Talazoparib in Patients With Triple-Negative Breast Cancer
NCT Number	NCT03901469
Document Date	26 May 2022

CLINICAL STUDY PROTOCOL	
TITLE	A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer
INVESTIGATIONAL NEW DRUG NUMBER	USA: 141108 China (for Expansion phase only): JXHL2000118, JXHL2000119
EUDRACT NUMBER	2018-003906-26
STUDY DRUGS	ZEN003694, Talazoparib
PROTOCOL NUMBER	ZEN003694-004
SPONSOR	Zenith Epigenetics Ltd.
SPONSOR'S HEAD OFFICE	Suite 300, 4820 Richard Road SW Calgary, Alberta Canada T3E 6L1
SPONSOR'S REPRESENTATIVE US OFFICE	[redacted]
SPONSOR'S MEDICAL MONITOR US OFFICE	[redacted]
CO-SPONSOR (Expansion phase, China only)	Newsoara Biopharma Co. Ltd. Room 809, 999 West Zhongshan Road Shanghai 200051, China
PROTOCOL DATE	Amendment 6 26 May 2022

Confidentiality Statement

This document contains proprietary and confidential information of the Sponsors Acceptance of this document constitutes agreement by the recipient that no previously unpublished information contained herein will be published or disclosed without the prior written approval of the Sponsors with the exception that this document may be disclosed to study personnel under your supervision who need to know the contents for conducting the study and appropriate Ethics Committees/Institutional Review Boards under the condition that the personnel have agreed to keep this information confidential. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, the Sponsors shall be promptly notified of any such disclosure.

LIST OF ABBREVIATIONS AND ACRONYMS

5-HT3	5-hydroxytryptamine type 3
ABC	ATP-binding cassette
ADC	Antibody drug conjugate
ADL	Activities of daily living
ADT	Androgen deprivation therapy
AE	Adverse event
AML	Acute myeloid leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
ASCO	American Society of Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve, from time zero to infinity
AUC_{0-24}	Area under the curve, from time zero to 24 hours
AUC_{0-last}	Area under the curve, from time zero to last time point with a quantifiable level of drug
BCL2	B-cell lymphoma 2
BCL2L1	B-cell lymphoma 2-like 1
BCRP	Breast cancer resistance protein
BET	Bromodomain and extra-terminal motif
BETi	BET bromodomain inhibitor
BICR	blinded independent central review
BID	Twice Daily
BM	bone marrow
BRCA1	Breast cancer 1 gene
BRCA2	Breast cancer 2 gene
BRCA1/2 wt	BRCA1 and BRCA2, wild-type
BRD2	Bromodomain-containing protein 2
BRD3	Bromodomain-containing protein 3
BRD4	Bromodomain-containing protein 4
BRDT	Bromodomain-testis-specific containing protein T
BUN	Blood urea nitrogen
C_{max}	Maximum or peak concentration
C_{min}	Minimum or trough concentration
C_{ss}	Concentration steady-state
CAP	College of American Pathologists
CBC	Complete blood count
CCR1	Chemokine (C-C motif) receptor 1
CDMS	Clinical data management system
CI	Confidence interval
[redacted]	[redacted]
CNS	Central nervous system

CR	Complete response
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CTC(s)	Circulating tumor cell(s)
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP1A2	Cytochrome P450, family 1, subfamily A, polypeptide 2
CYP2C8	Cytochrome P450, family 2, subfamily C, polypeptide 8
CYP2C9	Cytochrome P450, family 2, subfamily C, polypeptide 9
CYP2C19	Cytochrome P450, family 2, subfamily C polypeptide 19
CYP3A4	Cytochrome P450, family 3, subfamily A, polypeptide 4
CYP17A1	Cytochrome P450, family 17, subfamily A, polypeptide 1, or steroid 17-alpha-hydroxylase/17,20 lyase
DC	Dose confirmation
DDI	Drug-drug interaction
DDR	DNA damage response/repair
DE	Dose escalation
dL	Decilitre
DLT	Dose-limiting toxicity
DMP	Data management plan
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA
DOR	Duration of response
[redacted]	[redacted]
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFD	embryo-fetal development
ER	Estrogen receptor
ERG	V-Ets avian erythroblastosis virus E26 oncogene
ETS	E26 transformation-specific
ETV1	ETS translocation variant 1
FDA	Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practice
gBRCA1/2m	Germline BRCA1 or BRCA2 mutation
GI	Gastrointestinal
GLP	Good Laboratory Practice
GPR183	G Protein-Coupled Receptor 183
GR	Glucocorticoid receptor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose

HER2	Human epidermal growth factor receptor 2
hERG	Human ether-à-go-go related gene (an ion channel found in cardiac cell membranes)
HIST2H2BE	Histone gene cluster 1, H2BE histone family member E
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HPBL	human peripheral blood lymphocytes
HR	Homologous recombination
HRD	Homologous recombination deficiency
[redacted]	[redacted]
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IL1RN	Interleukin 1 receptor antagonist
INR	International normalized ratio
IQR	interquartile range
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram(s)
L	Litre
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LD	Longest diameter
LDH	Lactate dehydrogenase
mCRPC	Metastatic castration-resistant prostate cancer
mg	Milligram(s)
min	Minute(s)
mm^3	Cubic milimeter
MMS	methyl methane sulfonate
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
msec	Millisecond(s)
MTD	Maximum tolerated dose
MUGA	Multigated acquisition (scan)
MYC	V-Myc avian myelocytomatosis viral oncogene homolog
NCI	National Cancer Institute
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ng	Nanogram(s)
NHEJ	Non-homologous end joining
NUT	NUT gene that codes for a protein in germ cells
[redacted]	[redacted]
ORR	Objective response rate
PARPi	Poly adenosine diphosphate ribose polymerase inhibitor
PBMC	Peripheral blood mononuclear cell
PCT	physician's choice treatment

PD	Pharmacodynamics
PD	Progressive disease
PDX	Patient derived xenograft
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PR	Partial response
PR	Progesterone receptor
PRES	Posterior reversible encephalopathy syndrome
PRN	Pro re nata (when necessary)
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval corrected by the Fridericia correction formula
Rac	Accumulation ratio
RAD51	Gene involved in homologous recombination and repair of DNA
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small-cell lung cancer
SD	Stable disease
SLC	Solute carrier
SRSD	single reference safety document
STD_{10}	Severely toxic dose in approximately 10% of animals
SUSAR	Suspected unexpected serious adverse event
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum concentration
TFS	tumor-free survival
TGI	Tumor growth inhibition
TNBC	Triple negative breast cancer
TROP-2	Tumor-associated calcium signal transducer 2
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal

Table of Contents

LIST OF TABLES

LIST OF APPENDICES

2. SYNOPSIS

A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer
PROTOCOL NUMBER: ZEN003694-004
STUDY PHASE: Phase 2
INVESTIGATIONAL DRUG: ZEN003694
OBJECTIVES: ***Primary*** ***Part 1*** • To determine the safety, tolerability, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic triple-negative breast cancer (TNBC) ***Part 2*** • To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC ***Expansion*** • To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative (<5%) at the time of initial breast cancer diagnosis and who have received TROP2-ADC therapy in the unresectable locally advanced or metastatic disease setting. ***Secondary*** ***Part 1*** • To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib • To evaluate the effects of ZEN003694 and talazoparib on mRNA expression of pharmacodynamic markers • To evaluate the clinical activity of ZEN003694 in combination with talazoparib by radiographic response rate and progression-free survival • To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life ***Part 2*** • To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib

- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

Expansion

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative at the time of initial breast cancer diagnosis and who have not received TROP2-ADC in the unresectable locally advanced or metastatic disease setting
- To evaluate the ZEN003694 monotherapy in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative at the time of initial breast cancer diagnosis and who may or may not have received prior TROP2-ADC.
- To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib
- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib
- To determine the effect of ZEN003694 and talazoparib patient reported health status and quality of life

Exploratory

Parts 1 and 2; and Expansion

- [redacted]

STUDY DESIGN:

Part 1

Part 1 is an open label, non-randomized, dose escalation of ZEN003694 in combination with talazoparib in patients with TNBC. A standard 3+3 cohort design will be utilized. Cohorts of 3 patients and up to 6 patients will be enrolled at each dose level, and each patient will participate in only one cohort. Each cycle will be 28 days in duration. Patients at each dose level will be treated and observed through the end of the first 28-day cycle before treatment of patients at the next higher dose level can begin.

Dose escalation will continue after all patients enrolled within a cohort have completed the 28-day Cycle 1 DLT observation period with either 0 of 3 patients, or no more than 1 out of 6 patients in a cohort experiencing a DLT. Dose escalation decisions will be made based on clinical safety and (when available) PK data (maximum or peak concentration [Cmax] and area under the curve [AUC]) after review by the Investigators and Zenith. If a DLT is observed in 1 of 3 patients in a cohort, 3 additional patients will be enrolled into that cohort. If 1 of 6 patients in a cohort experiences a DLT, then dose escalation may continue in the next cohort or the MTD of the combination can be declared. If ≥ 2 of 3 – 6 patients experience DLTs within a cohort, then the MTD will be considered to have been

exceeded and further dose escalation will cease. In this case, if fewer than 6 patients have been enrolled at the previous dose level, that cohort will be expanded to 6 patients to confirm the MTD. Should the MTD of the combination be exceeded at Dose Level 1, a cohort may be explored with a reduced dose of ZEN003694 or talazoparib. Cohort management is summarized below.

Number of Patients with Dose-limiting Toxicity	Action
0 of 3 or 1 of 6	Dose escalate to next cohort
1 of 3	Add 3 more patients
1 of 6	Proceed to next dose level
≥ 2 of 3 or ≥ 2 of 6	Add 3 more patients in the next lower dose level if only 3 patients were treated in the next lower dose. If 6 patients were treated at the next lower dose level and no more than one patient had DLT, then the next lower dose is the MTD.

Enrollment in the dose escalation part of the study will commence with a 48 mg oral once daily dose as the starting dose for ZEN003694 in combination with a 1 mg oral once daily dose of talazoparib. The dose of ZEN003694 will be held constant throughout Cycle 1, however doses may be held for the management of toxicity. The dose of talazoparib may be held and reduced from the initial 1.0 mg dose in 0.25 mg increments in accordance with the talazoparib label and by agreement with Zenith. Dose escalation/de-escalation of ZEN003694 will proceed per the schema below unless intervening toxicity is observed. Alternative dosing schedules may be evaluated based on the evaluation of clinical safety and upon agreement of the Investigators and Zenith. Alternative dosing schedules may include intermittent dosing that could necessitate a change in the cycle duration from 28 days to 21 days.

Dose Level	**ZEN003694 (mg)****	**Fold Increase from Prior Dose Level**
-1	36	0.75
1	48	--
2	72	1.50
** Dose de-escalation from 48 mg is allowed and additional dose levels may be explored based on safety and at the discretion of the Sponsor.		

No intra-patient dose escalation is allowed during the first two cycles of therapy. If a patient has not experienced any Grade 2 or higher drug-related AEs after three cycles, dose escalation up to the highest ZEN003694 dose currently declared tolerable will be allowed and further intra-patient dose escalation(s) will be determined on a cycle-by-cycle basis at the discretion of the Investigators and with approval by the Sponsor.

Investigator/Sponsor teleconferences will be held during the dose escalation phase to discuss any suspected DLTs that have occurred in patients within each cohort. The frequency of the teleconference calls will be determined by the rate of enrollment, data review, frequency of DLT notifications, discussions with investigational sites and other factors. Approximately one week after the last patient in a dose cohort completes Cycle 1 and prior to enrolling in the next dose level, the

Investigators and Sponsor will review toxicities and available PK (e.g., C_{max} and AUC) from the current cohort of the study during a teleconference call.

Definition of Dose-limiting Toxicity

Determination of DLT will be made during the first 28 days of treatment (i.e., Cycle 1) in the dose escalation phase. Toxicity will be graded and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. A DLT is defined as a clinically significant AE or laboratory abnormality that is considered possibly, probably or definitely related to study drug and which meets any of the following criteria:

- Grade 3 or greater non-hematologic clinical toxicity with the exception of a) Grade 3 nausea or Grade 3/4 vomiting or diarrhea unless persisting more than 72 hours despite maximal medical therapy and b) Grade 3 or 4 amylase or lipase elevations that are not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 or greater fatigue for at least 1 week
- Grade 4 anemia
- Grade 4 neutropenia lasting more than 5 days
- Grade 3 or greater febrile neutropenia (temperature ≥ 38.5ºC)
- Grade 4 thrombocytopenia; or Grade 3 thrombocytopenia with clinically significant bleeding; or any requirement for platelet transfusion
- Grade 3 or 4 electrolyte abnormality lasting more than 72 hours, unless the patient has clinical symptoms, in which case all Grade 3 or 4 electrolyte abnormalities regardless of duration will be considered a DLT
- Any other Grade 3 or 4 laboratory abnormality that requires hospitalization
- An ALT or AST ≥ 3x ULN with concomitant total bilirubin > 2x ULN, and serum alkaline phosphatase ≤ 2x ULN (Hy's Law). For patients with hepatic metastases, AST or ALT >8xULN or AST or ALT >5x ULN for ≥14 days
- Any Grade 3 or 4 visual symptoms
- Any toxicity that results in more than 25% of missed doses during Cycle 1 of the 28-days of treatment, with the exception of a dose hold for Grade 3 thrombocytopenia, in which case a dose hold of both talazoparib and ZEN003694 for 10 consecutive days in Cycle 1 will be allowed and not considered a DLT . For an intermittent schedule of 2-weeks on/1-week off, if any toxicity results in more than 2 missed doses during the 2-week treatment period the toxicity would be considered a DLT.
- In the situation where toxicity requires withholding study drugs following the receipt of at least 75% of scheduled dosing during Cycle 1: Failure to begin Cycle 2 within 1 week of the scheduled start date due to ongoing toxicity.

All patients experiencing a DLT must discontinue dosing with ZEN003694 and talazoparib, except in the event that the DLT is thrombocytopenia, in which case patients may be re-challenged with ZEN003694 and talazoparib at doses agreed upon with the Sponsor if platelets recover to at least

75,000/µL within a 10-day dose hold. All patients who discontinue treatment must complete the Safety Follow-up visit prior to discontinuation from the study.

Determination of evaluability will be made during the first 28 days of study treatment (i.e., Cycle 1) in the dose escalation phase. Patients who miss more than 25% of ZEN003694 and talazoparib doses (except in the case of a dose hold for thrombocytopenia where 10 consecutive days of missed doses are allowed) or fail to begin Cycle 2 within 1 week of the scheduled start date for reasons other than drug-related toxicity will be considered unevaluable and will be replaced.

Definition of the Maximum Tolerated Dose

The MTD is defined as the highest dose level of ZEN003694 in combination with talazoparib at which no more than 1 of 6 patients experiences a DLT during the first cycle of therapy.

Definition of the Recommended Phase 2 Dose

The RP2D as determined in Part 1 of the study is defined as the dose level of ZEN003694 in combination with talazoparib recommended for further clinical study. The RP2D may be the same as the MTD or modified from the MTD based on assessment of overall exposure, safety experience in Cycle 2 and beyond, PD and clinical benefit data in this study.

Part 2: Simon 2-Stage

Stage 1:

Once an RP2D of ZEN003694 in combination with talazoparib has been determined in the dose escalation part of the study, 17 patients will be enrolled in Stage 1 of a Simon 2-Stage design (Simon, 1989) for evaluation of objective response (complete response (CR), partial response (PR), or stable disease (SD) for ≥ 4 cycles) by RECIST 1.1 (Eisenhauer, et al., 2009). If there are ≥4 objective responses the study will proceed to Stage 2. If there are <4 responses, the study will be stopped.

Stage 2:

If at least 4 patients in Stage 1 have an objective response (CR, PR or SD for ≥ 4 cycles) by RECIST 1.1, 20 patients will be enrolled in Stage 2 of the Simon 2-Stage design. Patients will receive daily RP2D doses of ZEN003694 (48mg) in combination with 0.75 mg talazoparib. Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study.

Expansion

The expansion of the study will be implemented under amendment following the determination of the RP2D of ZEN003694 in Part 1 and after meeting the primary endpoint of clinical benefit rate of 35% in Part 2. The study will be expanded to enroll an additional 120 patients with locally advanced or metastatic TNBC that is without germline BRCA1/BRCA2 mutations and was hormone receptor negative (<5%) at the time of initial breast cancer diagnosis.

Expansion Cohort A: Combination Treatment in post-TROP2-ADC patients: Eighty (80) patients will receive daily RP2D doses of ZEN003694 (48mg QD) in combination with talazoparib (0.75mg QD). Patients may continue receiving ZEN003694 in combination with talazoparib until

radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from the study.

Expansion Cohort B: ZEN003694 Monotherapy: As mandated by the FDA to assess any potential single agent ZEN003694 activity, ten (10) patients will initially receive daily doses of 48mg ZEN003694 as monotherapy with the option to cross-over to combination treatment of 48mg ZEN003694 plus 0.75mg talazoparib at the time of disease progression (but no sooner than after 6 weeks of monotherapy). Patients in the cross-over group may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study.

Expansion Cohort C: Combination Treatment in TROP2-ADC naïve patients: Thirty (30) patients who have not received prior TROP2-ADC will receive daily RP2D doses of ZEN003694 (48mg QD) in combination with talazoparib (0.75mg QD). Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from the study.

NUMBER OF SITES:

Approximately 9 sites in the United States; 4 sites in Western Europe; and 5 sites in China (Expansion only).

NUMBER OF PATIENTS:

In Parts 1 and 2, up to approximately 52 evaluable subjects will be enrolled in the study with up to approximately 16 patients in Part 1 dose escalation and up to 37 patients in Part 2, a Simon 2-Stage evaluation of objective response.

In the Expansion part of the study, approximately 80 evaluable patients (in US and EU) will be enrolled in Cohort A (combination treatment in post-TROP2-ADC patients) and approximately 10 evaluable patients (in US and EU) will be enrolled in Cohort B (ZEN003694 monotherapy). Approximately 30 evaluable patients (in China only) will be enrolled in Cohort C (combination treatment in TROP2-ADC-naïve patients).

ESTIMATED STUDY DURATION:

The estimated study duration for Part 1 dose escalation is approximately 6 months. The estimated duration for Part 2 Simon 2-Stage is approximately 12 months. The estimated duration of the Expansion phase will be approximately 18 months.

ELIGIBILITY CRITERIA:

Inclusion Criteria

Patients must meet the following inclusion criteria to be eligible for the study.

1. Females or males age ≥ 18 years (at time of signing informed consent)
2. **Parts 1 and 2:** Histologically confirmed metastatic or recurrent, or locally advanced triple-negative breast cancer (estrogen receptor (ER) ≤10%; progesterone receptor (PR) ≤10%; HER2 negative by immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH)

   Expansion: Histologically confirmed metastatic or recurrent, or locally advanced triple-negative breast cancer as defined by the most recent American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.

3. Patient is not a candidate for endocrine based therapy, based on Investigator judgement
4. Have a history of progressive disease despite prior therapy
5. **Part 1**: Have had at least 1 prior cytotoxic chemotherapy.

   Part 2: Have had no more than 2 prior chemotherapy-inclusive regimens for locally advanced or metastatic disease, unless approved by the Sponsor (no limit on prior targeted anticancer therapies such as mechanistic target or rapamycin (mTOR) or CDK4/6 inhibitors, immune-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or VEGF.)

   Expansion Cohort A (combination treatment in post-TROP2-ADC patients): Have received TROP2-ADC therapy for unresectable locally advanced or metastatic disease.

   Expansion Cohort B (ZEN003694 monotherapy): Have had at least 1 prior systemic therapy for locally advanced or metastatic disease which may or may not have included TROP2-ADC therapy.

   Expansion Cohort C (combination treatment in TROP2-ADC-naive patients): Have had at least 1 prior systemic therapy for locally advanced or metastatic disease and who have not received prior TROP2-ADC therapy.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. **Part 2 and Expansion only**: Measurable disease per RECIST version 1.1
8. Adequate laboratory parameters at Screening including:
   a. **Parts 1 and 2:** Hemoglobin ≥ 10.0 gm/dL without transfusions during the 4 weeks prior to Screening. **Expansion:** Hemoglobin ≥ 9.0 gm/dL
   b. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   c. Platelet count ≥ 150,000/mm^3
   d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.0 x ULN or if liver function abnormalities due to liver metastases AST and ALT ≤ 5.0 x ULN
   e. Total bilirubin ≤ 1.5 x ULN (≤ 3.0 x ULN for subjects with known Gilbert's syndrome)
   f. Calculated (Cockcroft-Gault formula) or measured creatinine clearance ≥ 60 mL/min
   g. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN
9. Female subjects may be enrolled if they are not of childbearing potential, permanently sterile or who are post-menopausal, defined as no menses for at least 1 year without an alternative medical cause and FSH levels in the post-menopausal range. Female subjects of childbearing potential may be enrolled if they consistently and correctly use a highly effective form of contraception from the time point of study drug administration until at least 7 months thereafter. Highly effective forms of contraception include: combined (estrogen and progestogen hormonal contraceptives (oral, intravaginal, transdermal)

associated with inhibition of ovulation; progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence. Female subjects should not donate eggs from the time point of study drug administration until at least 7 months thereafter.

10. Males with partners of childbearing potential may be enrolled if they use a condom when having sex with a pregnant woman or with a non-pregnant female of childbearing potential from 21 days before the first dose of study drug through 4 months after the last dose of study drug, and males should not donate sperm from the time point of study drug administration until at least 4 months thereafter. Contraception should be considered for a non-pregnant female partner of childbearing potential.

11. Females of childbearing potential must have a negative serum or urine pregnancy test before the first dose of study drug and must agree to pregnancy tests during the study.

12. Females may not be breast-feeding at the first dose of study drug, during study participation or through 7 months after the last dose of study drug.

13. Ability to swallow capsules and comply with study procedures

14. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures

Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

1. Documented germline mutations of BRCA1 or BRCA2

2. **Parts 1 and 2 only:** Evidence of disease progression during platinum treatment either in the neoadjuvant or in the metastatic setting. For patients receiving platinum in the neoadjuvant setting, at least 6 months must have elapsed between the last dose of platinum-based treatment and enrollment.

3. **Part 2 only:** Patients with inflammatory breast cancer

4. Current or anticipated use of medications known to be strong inhibitors or inducers of CYP3A4 or substrates of CYP1A2 with narrow therapeutic windows. Strong inhibitors, inducers or substrates must be discontinued at least 7 days prior to the first administration of study drug.

5. Current or anticipated use within 7 days prior to the first administration of study drug, or during the study, of strong P-gp inhibitors.

6. Use of oral Factor Xa inhibitors (i.e., rivaroxaban, apixaban, betrixaban, edoxaban otamixaban, letaxaban, eribaxaban) and Factor IIa inhibitors (i.e., dabigatran). Low molecular weight heparin is allowed.

7. Prior anticancer therapy (chemotherapy, radiation, hormone therapy, immunotherapy or investigational agent) within 3 weeks from the start of study drug (except for nitrosoureas

and mitomycin C within 6 weeks from start of study drug).

8. **Parts 1 and 2 only:** Radiation to >25% of the bone marrow
9. Treatment with a bone-targeted radionuclide within 6 weeks of first dose of study drug.
10. Have previously received an investigational BET inhibitor (including previous participation in studies with the Sponsor's drug, ZEN003694); except for patients in Expansion Cohort B who received ZEN003694 monotherapy and are eligible to cross-over to combination treatment
11. Prior treatment with a PARP inhibitor.
12. QTcF interval > 470 msec.
13. Insufficient recovery (i.e., has not recovered to at least Grade 1) from prior treatment-related toxicities except for alopecia, fatigue and Grade 2 neuropathy.
14. Non-healing wound, ulcer or bone fracture (not including a pathological bone fracture caused by a pre-existing pathological bone lesion).
15. **Parts 1 and 2 only**: Brain metastases not adequately treated and clinically stable (at the discretion of the Investigator) for at least 3 months prior to the start of study treatment, unless a shorter interval is approved by the Sponsor's Medical Monitor

    Expansion only: Progressive, symptomatic, or untreated brain metastases. CNS metastases treated definitively with surgery and/or radiation must be radiographically stable based on imaging at least 3 months after definitive treatment. CNS metastases requiring steroid doses equivalent to prednisone doses >10 mg daily or an increase in steroid doses due to CNS disease prior to consent are not eligible
16. **Expansion only:** Disease initially diagnosed with expression of estrogen receptor (ER) or progesterone receptor (PR) as ⩾5%
17. **Expansion only:** Patients treated with prior endocrine therapy
18. Known impaired cardiac function or clinically significant cardiac disease such as uncontrolled supraventricular arrhythmia, ventricular arrhythmia requiring therapy, or congestive heart failure (New York Heart Association functional class III or IV).
19. Myocardial infarction or unstable angina within 6 months prior to the first administration of study drug.
20. Known myelodysplastic syndrome.
21. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, or any other condition that could compromise safety or the patient's participation in the study,
22. Impairment of gastrointestinal function (i.e., diagnosis of malabsorption syndrome) that may significantly alter the absorption of ZEN003694 or talazoparib.

23. Other known active cancer requiring therapy at time of study entry or that progressed or required treatment within 3 years prior to starting study drug (except for skin basal cell carcinoma or squamous cell carcinoma or in situ cervical cancer).

24. Historically positive (screening tests not required) for human immunodeficiency virus (HIV); or hepatitis B virus (HBV) with currently active disease defined as hepatitis B surface antigen (HBsAg) positivity; or hepatitis C virus (HCV) unless previously treated and viral load is undetectable.

25. Major surgery other than diagnostic surgery, dental surgery or stenting within 4 weeks prior to the first administration of study drug.

26. Concurrent participation in another clinical investigational treatment trial with a systemic therapy

27. Any other reason that in the opinion of the Investigator would prevent the patient from completing participation or following the study schedule.

DOSE, REGIMEN AND ROUTE OF ADMINISTRATION:

ZEN003694

ZEN003694 will be supplied in capsules of two different dosage strengths: 12 mg and 48 mg.

The ZEN003694 starting dose for this study is 48 mg, administered orally once daily. Doses will be administered in 28-day cycles and should be administered with a full (8-ounce) glass of water at least 1 hour before eating or 2 hours after eating (fasting). The RP2D of 48 mg once daily will be administered in Part 2 and Expansion.

Talazoparib

Talazoparib will be supplied as oral capsules in strengths of 1.0 mg and 0.25 mg.

Talazoparib will be administered as a starting dose of 1 mg once daily in Part 1 to be taken at the same time as ZEN003694. The talazoparib dose of 0.75 mg once daily will be administered in Part 2 and Expansion.

STUDY ASSESSMENTS:

Safety

Safety will be assessed by periodic physical examinations, weight, ECOG performance status, vital signs, clinical laboratory assessments (hematology, serum chemistries, coagulation tests and urinalysis), 12-lead electrocardiogram (ECG) and monitoring of AEs (see Schedule of Assessments).

Pharmacokinetics

Plasma samples will be collected to assess the PK properties of ZEN003694 and its active metabolite, ZEN003791, and talazoparib. Plasma concentrations of ZEN003694, its active metabolite ZEN003791, talazoparib will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. Samples will be collected as indicated in the Schedule of Assessments.

Pharmacodynamics

Blood samples will be analysed for the effects of ZEN003694 and talazoparib on five PD mRNA markers. Samples for exploratory prognostic and/or predictive biomarkers in whole blood by ctDNA analyses and in tumor tissue by RNA-sequencing, DNA-sequencing and immunohistochemical staining will be collected for banking and possible future analyses in Simon 2-Stage and in the Expansion phase of the study. Tumor tissue will be obtained as indicated in the Schedule of Assessments.

Objective Responses

Tumor assessments and measurable disease is to be assessed per RECIST 1.1 guidance. Measurable disease must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by caliper measurement by clinical exam (lesions cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray
- Baseline measurements should be performed as close as possible to the treatment start and not more than 4 weeks before the start of treatment.

CT is the best and most reproducible method to measure lesions selected for response assessment. CT slice thickness should be 5 mm or less per RECIST 1.1. CT scans having slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Chest CT is preferred over Chest X-ray.

MRI is also acceptable in certain situations (e.g. for body scans).

Disease status should be assessed according to RECIST 1.1 at visits as indicated in the Schedule of Assessments.

STATISTICAL METHODS:

Sample Size Determination

Part 1: Dose escalation

A conventional algorithm (3+3 patients per dose level) will be used to identify the MTD, escalating on 0 of 3 or 1 of 6 DLTs, and de-escalating if 2 DLTs are encountered. The MTD will be the highest dose level at which 0 of 3 or 1 of 6 patients experience a DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT. With this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20%, and less than 50% chance of escalation if the true but unknown rate of DLT is higher than 30%.

Approximately 12 patients may be enrolled in the dose escalation phase of the study.

Part 2: Simon 2-Stage

Stage 1: 17 patients are planned to be enrolled at the MTD or RP2D in Stage 1 based on a null hypothesis that TNBC patients will have an overall response rate (ORR) of 20% and the study will target an ORR of 40%. For purposes of this study, the overall response rate (ORR) is more accurately defined as clinical benefit rate (CBR). CBR is defined as percentage of

patients with a confirmed RECIST 1.1 response or stable disease ≥4 cycles. Ho = 20 % will be tested against a one-sided alternative. (A CBR of 20% is not of clinical interest whereas a CBR of 40% warrants further investigation.) If there are less than 4 responses in the 17 patients enrolled, the study will be stopped.

Stage 2: 20 patients are planned to be enrolled if there are at least 4 responders in Stage 1. Ho will be rejected if there are ≥ 11 patients with a CBR in 37 patients. Type I error rate of 0.1 when the true response rate is 20% and power of 90% when the true CBR is 40% (target error rates 0.10 and 0.10); the probability of early termination is 0.55.

Expansion Cohort A: Combination Treatment (post-TROP2-ADC patients):

Expansion Cohort A will enroll patients with locally advanced or metastatic TNBC without germline BRCA1/BRCA2 mutations who have had prior treatment with TROP2-ADC for unresectable locally advanced or metastatic disease. Approximately 80 evaluable patients are planned to establish the ORR and further define the safety profile of the combination ZEN003694 and talazoparib. An observed ORR (by blinded independent central review) of at least 30% represents a significant improvement over current available therapies in this patient population. With 80 patients, 24 or more responders will provide an observed ORR of at least 30% and a lower limit of the 95% confidence interval above 20%. The RECIST v1.1 assessment of response will be assessed by an independent review committee.

Expansion Cohort B: ZEN003694 Monotherapy:

Expansion Cohort B will enroll patients with locally advanced or metastatic TNBC without germline BRCA1/BRCA2 mutations who have had two prior systemic treatments for locally advanced or metastatic disease. Approximately 10 evaluable patients are planned to assess the preliminary anti-tumor activity and provide additional information for the safety profile of ZEN003694.

Expansion Cohort C: Combination Treatment (TROP2-ADC-naïve patients):

Expansion Cohort C will enroll patients with locally advanced or metastatic TNBC without germline BRCA1/BRCA2 mutations who have not previously received TROP2-ADC and have had at least two additional prior systemic therapies for locally advanced or metastatic disease. Approximately 30 evaluable patients are planned to establish the ORR and further define the safety profile of the combination ZEN003694 and talazoparib.

Statistical Analyses

Part 1: Dose escalation

The primary statistical analysis of the data will be descriptive in nature. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by patient counts and related percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and

means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

Based on the characteristics of the study design and lack of a concurrent control arm, formal testing of treatment effects (i.e., inferential statistics) will not be performed. However, some measures will be summarized by both point estimates and the associated 95% confidence intervals.

Part 2: Simon 2-Stage

The primary outcome measures in the Simon 2-Stage phase of the study will be clinical benefit rate (CBR) defined as a complete response, partial response or stable disease (≥ 4 cycles) by RECIST v1.1. CBR and 95% confidence interval will be calculated using the exact binomial model.

Secondary outcome measures will include:

- Progression-free survival (PFS): defined from randomization to documented disease progression or death
- Duration of response (DOR): for confirmed responses, defined as the duration from the time of first response (CR or PR) until radiographic disease progression or death.
- Pharmacokinetics (PK): $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$,, Cmax, Cmin, Tmax, and T½ of ZEN003694, ZEN003791, and talazoparib during the first 2 treatment cycles
- Incidence of Adverse Events: from time of signing informed consent
- Quality of Life (EORTC Quality of Life Questionnaires, QLQ-C30 and QLQ-BR23)

Expansion Cohort A: Combination Treatment (post-TROP2-ADC patients)

The primary outcome measure in Expansion Cohort A (Combination Treatment) will be objective response rate (ORR) per RECIST v1.1 as measured by independent central review.

Secondary outcome measures will include:

- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression free survival (PFS)
- Safety analyses will include, but are not limited to, AEs, laboratory abnormalities, ECG evaluations, and vital signs
- Pharmacokinetics: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$,, Cmax, Cmin, Tmax, and T½ of ZEN003694, ZEN003791, and talazoparib during the first 2 treatment cycles
- Quality of Life (EORTC Quality of Life Questionnaires, QLQ-C30 and QLQ-BR23)

Expansion Cohort B: ZEN003694 Monotherapy

In discussions with the FDA, if no more than 1 patient (out of the 10 evaluable patients enrolled) have a confirmed objective response to ZEN003694 monotherapy, it can be concluded that ZEN003694 as a monotherapy has no clinical benefit.

Expansion Cohort C: Combination Treatment (TROP2-ADC-naïve patients)

Outcome measures for Cohort C will include:

- Objective response rate (ORR) per RECIST v1.1 as measured by investigator
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression free survival (PFS)
- Safety analyses will include, but are not limited to, AEs, laboratory abnormalities, ECG evaluations, and vital signs
- Pharmacokinetics: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$,, Cmax, Cmin, Tmax, and T½ of ZEN003694, ZEN003791, and talazoparib during the first 2 treatment cycles
- Quality of Life (EORTC Quality of Life Questionnaires, QLQ-C30 and QLQ-BR23)

Table 1: Schedule of Assessments

	Screening (28 Days prior to C1D1)^	Cycle 1** (Days 1 – 28)	Cycle 2** (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [p]	End of Treatment [q]	Safety Follow-up [r]
Informed Consent	X						
Medical, Surgical, Cancer History, Prior Cancer Treatments and Demographics	X						
Physical Examination, Vital Signs, Weight, Height, ECOG Status [a]	X	Days 1*, 8, 15, 22**	Days 1, 15	Day 1	X	X	X
Hematology and Serum Chemistry [b]	X	Days 1*, 8, 15, 22**	Days 1, 8, 15, 22**	Days 1, 15	X	X	X
Creatinine clearance, calculated [b]	X						
Coagulation Tests [c]	X	Days 1*, 15	Day 1	Day 1	X		
Urinalysis [d]	X	Day 1*	Day 1	Day 1	X	X	X
Quantitative Urinary Analysis [d]	X	Day 1*	Day 1	Day 1	X	X	X
Pregnancy test [e]	X	Day 1	Day 1	Day 1		X	
12-Lead Electrocardiogram [f]	X	Days 1*	Day 1	Day 1 (at C3 and every 2 cycles)			
[redacted]	[redacted]						
[redacted]		[redacted]	[redacted]			[redacted]	
Tumor Assessments (RECIST) [h]	X		**EXPANSION (Cohorts A, B, C):** Cycle 2, Day 15 and every 6 weeks	**PARTS 1 & 2** (every 8 weeks): Day 1 (at C3 and every 2 cycles) **EXPANSION:** (every 6 weeks) **Day 1** (at C4, C7, C10, C13, C16, C19, etc.); **and Day 15** (at C5, C8, C11, C14, C17, C20, etc.)		X	
BRCA1/2 mutation status [i]	X						
Pharmacokinetics [j]		Part 1 only Days 1, 15	Days 1, 15				

	Screening (28 Days prior to C1D1)^	Cycle 1** (Days 1 – 28)	Cycle 2** (Days 1 – 28)	Cycle 3 Onward (Days 1 – 28)	Unscheduled Visit [p]	End of Treatment [q]	Safety Follow-up [r]
BETi and PARPi PD marker mRNA [k] (in Part 1 only)		Day 1					
ctDNA [l] (for possible future analysis)		Day 1		Day 1 (at C3 only)		X	
Archival Tumor Tissue Collection [m]	X						
Tumor Biopsy Collection [m]	X	**Parts 1 & 2**: Days 8-10 **Expansion:** Days 8-14 [m]		Day 1 (at C3 only) (if not obtained in cycle 1)		X [m]	
ZEN003694 Administration [n]		Days 1 through 28 of each cycle					
Talazoparib Administration [n]		Days 1 through 28 of each cycle (except for patients taking ZEN003694 monotherapy in Expansion Cohort B)					
Global Health Status / Quality of Life [o]	X	Day 1	Day 1	Day 1		X	
Adverse Events		Days 1, 8, 15, 22**	Days 1, 15	Day 1	X	X	X
Prior/Concomitant Medications	X	Days 1, 8, 15, 22**	Days 1, 15	Day 1	X	X	X

TABLE 1 Footnotes:

All clinic visits should occur within ± 3 days of the scheduled visits listed in Table 1 and tests/samples should be obtained pre-dose unless specified otherwise.

General Notes:

- **The visits in Cycle 2 (Days 8 and 22) and in Cycle 3 and onward (Day 15): will only include blood draws for safety laboratory testing. The tests on C2D8, C2D22 and the Day 15 visit of Cycle 3 and onwards may optionally be drawn at a laboratory local to the patient's home and may be drawn in the morning before or after the patient has taken his/her dose.**
- **During the COVID-19 pandemic:**
  - **Telephone visits may be performed at the following visits: Cycle 1, Days 8 and 22; and Cycle 2, Day 15.**
  - **The following prospective deviations are allowed for the non-assessment of the following only if a patient is unable to attend an in-clinic visit: physical examinations, vital signs, weight, ECOG, PK blood draws, PD blood draws, and biopsies.**
  - **In-clinic visits are mandatory at Cycle 1, Days 1 and 15; and on Day 1 of all Cycles**.

***** Perform laboratory tests at Cycle 1 Day 1 (C1D1) only if Screening tests were performed more than 7 days prior to C1D1 visit

**** If intermittent dosing is implemented and/or if there is a need to change the cycle duration from 28 days to 21 days, the Day 22 assessments will not be required.**

^ **Cross-over Expansion Cohort B:** Patients enrolled in the Expansion Cohort B (ZEN003694 monotherapy) are allowed to cross-over to the combination treatment within 14 days after radiographic progression on ZEN003694 monotherapy has been established. Patients may cross-over to the combination treatment at the time of disease progression but no sooner than after 6 weeks of receiving ZEN003694 monotherapy. Patients choosing to cross-over treatment must sign a new informed consent form and complete all screening assessments as those originally required for enrollment in Expansion Cohort B of the study. The schedule of study assessments for the cross-over patients will be identical to those for Expansion patients starting at C1D1 and throughout the study.

[a] Complete physical examination to be performed at the Screening visit and a symptom-directed physical examination thereafter. Height to be measured at the Screening Visit only. Vital signs: body temperature, blood pressure and heart rate.

[b] **Hematology:** complete blood count (CBC) with differential and absolute neutrophil count (ANC). **Serum chemistry:** albumin, alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, bicarbonate, total bilirubin, blood urea nitrogen (BUN or Urea), total calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), sodium, potassium, phosphorus and magnesium. **Creatinine clearance:** At screening only, to be calculated by Cockcroft-Gault formula. Note: The Day 8 and Day 22 hematology and chemistry tests in Cycle 2 do not need to occur prior to dosing. In Cycle 6 and onward, the Day 15 hematology and serum chemistry tests may be waived at the discretion of the Investigator if platelet counts are stable and there are no other laboratory concerns.

[c] **Coagulation tests**: prothrombin time (PT) or international normalized ratio (INR) and partial thromboplastin time (PTT, APTT acceptable)

[d] **Urinalysis**: dipstick with micro-analysis if clinically indicated. From the urine sample collected for standard urinalysis assessment, quantitative biochemical analyses of urinary protein, albumin and creatinine is also required along with the reporting of the protein:creatinine ratio and the albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory.

[e] **Pregnancy test**: At screening a serum or urine pregnancy test is required of all women of child-bearing potential only. A urine pregnancy test is to be performed on Day 1 of each cycle prior to administration of study treatment. If a urine pregnancy test is positive, study treatment must be interrupted and a serum pregnancy test performed.

[f] 12-lead electrocardiogram (ECG) to be performed. To be collected pre-ZEN003694 and talazoparib doses on C1D1, C2D1 and C3D1 and every 2 cycles onward. Triplicate ECGs are to be collected if QTc>500msec. QTc is to be measured using Fridericia's formula.

[redacted]

[h] Tumor assessment (preferably by CT scan) to include whole body imaging with cross-sectional imaging of the chest/abdomen/pelvis. Use of IV contrast is required unless contra-indicated. Magnetic resonance imaging (MRI) may be substituted for computed tomography (CT) per Investigator's discretion. Imaging may be scheduled up to 7 days prior to the scheduled clinic visit day. The EOT tumor assessment is to be performed only if the EOT visit is > 6 weeks from the time of the prior tumor assessment. **Tumor Assessments in EXPANSION phase**: In the Expansion phase of the study, tumor assessments will be performed every 6 weeks. Thus, as a cycle is every 28 days, tumor assessments are to occur at Day 15 in Cycles 2, 5, 8, 11, 14, 17, 20, etc.; **and** at Day 1 in Cycles 4, 7, 10, 13, 16, 19, etc.

[i] Germline BRCA1/2 mutation status: Parts 1 and 2: For patients who have prior documentation of gBRCA mutation status, a blood sample for gBRCA testing is not required to be collected nor shipped to Myriad Genetics (for US and EU samples). If prior testing of gBRCA status has not been performed, either a blood sample can be collected and shipped to Myriad Genetics (for US and EU samples) or if your Institution has a qualified NGS testing panel a blood sample may be tested using your platform. Samples collected in China will have gBRCA1/2 testing performed at a laboratory approved by the Sponsor. Reports showing the panel of genes tested to establish BRCA1/2 mutation status are to be provided to the Sponsor. **In Cohort A EXPANSION phase only:** Germline BRCA1/2 mutation status: If prior testing of gBRCA has not been performed, a blood sample will be collected and shipped to Myriad Genetics at ambient temperature. If prior documentation of BRCA1/2 mutation status by BRACAnalysis CDx performed by Myriad Genetics is not available, a screening blood sample will be collected and frozen for retrospective analysis in batches. For patients who have prior documentation of BRCA mutation status by BRACAnalysis CDx, a blood sample for possible retrospective BRCA germline testing should NOT be collected. In cohort B and C EXPANSION phase, BRCA1/2 mutation status may be determined by Myriad Genetics or other Sponsor approved laboratory.

[j] Blood (plasma) for pharmacokinetic (PK) profile of ZEN003694, ZEN003791 and talazoparib will be collected as specified below: The pre-dose PK sample collections should be collected at least 20 hours after the previous day of dosing talazoparib.

Part 1 (Dose escalation) PK for ZEN003694 and ZEN003791:

C1D1: pre-ZEN003694 and talazoparib doses
C1D1: 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and talazoparib doses
C1D15: pre-ZEN003694 and talazoparib doses
C2D1: pre-ZEN003694 and talazoparib doses
C2D1: 1 hour (±5 min), 2 hours (±10 min), and 4 hours (±15 min) post-ZEN003694 and talazoparib doses
C2D15: pre-ZEN003694 and talazoparib doses

Part 1 (Dose escalation) PK for talazoparib:

C1D15: pre-ZEN003694 and talazoparib doses
C2D1: pre-ZEN003694 and talazoparib doses
C2D15: pre-ZEN003694 and talazoparib doses

Part 2 (Simon 2-stage) and Expansion Cohorts A, B, C: PK for ZEN003694 and ZEN003791:

C2D1: pre-ZEN003694 and talazoparib doses
C2D1: 1 hour (±5 min), 2 hours (±10 min), and 4 hours (±15 min) post-ZEN003694 and talazoparib doses
C2D15: pre-ZEN003694 and talazoparib doses

Part 2 (Simon 2-stage) and Expansion Cohorts A and C: PK for talazoparib:

C2D1: pre-ZEN003694 and talazoparib doses
C2D15: pre-ZEN003694 and talazoparib doses

[k] Blood samples for BET inhibitor and PARP inhibitor PD marker mRNA expression will be collected in Part 1 only:

- C1D1: pre-ZEN003694 and talazoparib doses
- C1D1: 2 hours (±15 min), 4 hours (±15 min), 6 hour (±15 min) and 8 hour (±15 min) post-ZEN003694 and talazoparib doses

[l] Blood samples (whole blood) for ctDNA assessments, US and EU sites only. (Samples are to be collected for possible future analysis)

- C1D1 pre-ZEN003694 and talazoparib doses
- C3D1 pre-ZEN003694 and talazoparib doses
- End of Treatment Visit

[m] Fresh tumor biopsy collections are mandatory in US and EU only, if the tumor is accessible. During each biopsy procedure, 2-4 tumor tissue cores (optimally 4 cores should be collected: 2 frozen cores, 2 formalin fixed cores) should be obtained. Biopsy procedures are to be scheduled at Screening and at the on-treatment visit occurring either at C1D8 or C3D1 (if biopsy was not obtained in Cycle 1). If possible, an End of Treatment (EOT) biopsy is to be optionally collected at the time of progression. The on-treatment biopsy is at either a) In **Parts 1 and 2**: C1D8, C1D9, or C1D10, if the biopsy is collected from a palpable lesion (or from other lesions, at the Investigator's discretion); In **Expansion phase**, biopsies are to be collected for patients in the US and EU between C1D8 and C1D14; **or** b) within ±14 days of the C3D1 visit (if biopsy was not obtained in Cycle 1). Please note: biopsies will NOT be collected for patients in China. The screening biopsy may be performed up to 6 weeks prior to the first dose of study drug. The on-treatment biopsy should be collected 2-4 hours after ZEN003694 dosing, if possible, and should be collected from the same tissue location as the screening biopsy. Biopsies taken at screening or at the on-treatment visit should not be taken from a recent prior irradiated site. Archival tumor tissue slides (either at least 10 slides preferably from a recent metastatic biopsy or a tissue block), if available and with the patient's consent, will be collected in Parts 1 and 2, and in the Expansion phase, in Cohort A only. The pathology and molecular report for the archival tissue sample is to also be collected.

[n] ZEN003694 and talazoparib are to be taken orally on a daily basis and at the same time during the course of treatment. Patients will be asked to maintain a dosing diary.

[o] Global Health Status and Quality of Life to be measured by EORTC QLQ-C30; EORTC QLQ BR23

[p] During any Unscheduled visit; the physical examination, vital signs, weight, hematology, coagulation tests, serum chemistry, urinalysis, concomitant medications and AEs are to be performed. Any other clinically indicated assessments are also to be performed.

[q] At the End of Treatment visit if a subject's dose was held and treatment was not resumed after a two week period, the scheduling of the EOT visit from the date of last study drug is extended from 7 days to 14 days (±3 days).

[r] The Safety Follow-Up Visit should be completed 30 days (±3 days) after the End of Treatment visit or prior to the subject beginning a new anti-cancer treatment, whichever occurs first. If the subject begins a new anti-cancer treatment within 7 days following the End of Treatment visit, the Safety Follow-Up visit is not required

3. BACKGROUND

3.1 BET Inhibitors in Cancer

The bromodomain and extra terminal domain (BET) proteins comprise four closely related bromodomain-containing proteins (BRD2, BRD3, BRD4, and BRDT) that are a subset of the larger family of 46 bromodomain-containing proteins. The BET proteins are epigenetic readers that regulate transcription in part by binding acetylated lysines on histones and transcription factors. BET proteins have generated a lot of interest due to their potential to target the expression of oncogenes including V-Myc avian myelocytomatosis viral oncogene homolog (MYC), B-cell lymphoma 2 (BCL-2) and B-cell lymphoma 2-like 1 (BCL2L1) as well as for their involvement in mediating drug resistance (**Dawson, et al., 2012; Dawson, et al., 2011**; **Goodell & Godley, 2013; Neff & Armstrong, 2013; Shi & Vakoc, 2014; Zuber, et al., 2011**). Expression of multiple oncogenes is also driven by BRD4 recruitment at super-enhancers, providing a rationale for the activity of BET inhibitors (BETi) beyond the MYC family (**Hnisz, 2013; Loven, et al., 2013**). All of the BETi currently in clinical trials target all members of the BET family, although the anti-proliferative activity of BETi in cancer cells may be mediated, in large part, through inhibition of BRD4 (**Filippakopoulos & Knapp, 2014**).

In vitro cell line analyses have shown that targeting BET proteins leads to inhibition of tumor growth in multiple cancer types, including both solid tumors and hematological malignancies through cell cycle arrest, and induction of senescence and apoptosis.

3.2 PARP inhibitors in Cancer

Poly-ADP ribose polymerases (PARP) are a family of enzymes that catalyze the addition of poly-ADP ribose moieties to histones and other proteins to regulate various cellular processes, including gene transcription and DNA repair. PARP1 and PARP2 play important roles in DNA repair (**Schrieber, et al., 2006; Curtin, et al., 2005**). Following DNA damage, PARP1 and PARP2 bind to single stranded DNA breaks, cleave nicotinamide adenine dinucleotide, and attach multiple ADP ribose units to the target protein, including itself (**Gibson & Kraus, 2012; Schreiber, et al., 2002; Amé, et al., 1999; Johansson, 1999**). The outcome is a highly negatively charged protein, which leads to the unwinding of the DNA strands and recruitment of proteins to repair the damaged DNA through the base excision repair process. When PARP1 and PARP2 are inhibited, single strand DNA breaks persist, resulting in stalled replication forks and conversion of single strand breaks into double strand breaks. These breaks must be repaired by homologous recombination or nonhomologous end joining or they may become lethal. Thus, inhibition of PARP catalytic activity results in synthetic lethality as defects in homologous recombination DNA repair prevent double strand breaks from being repaired, thereby killing the cell, including cancer cells. In addition, PARP inhibitors bind to PARP DNA complexes (i.e., become trapped); thereby inhibiting DNA repair, replication, and transcription, which may also be is cytotoxic to cancer cells. Although other PARP inhibitors possess both activities (i.e., inhibition of PARP catalytic activity and PARP trapping), in vitro studies demonstrated that talazoparib is a more potent PARP trapper than other PARP inhibitors in clinical development, a property that has been associated with significant cytotoxicity in preclinical models (**Johansson, 1999; Hopkins, et al., 2015; Lord**

& Ashworth, 2017). Cancer cells with deficiencies in homologous recombination (HR) DNA repair, namely with mutations in either BRCA1 or BRCA2, are sensitive to inhibition of PARP, owing to their inefficacy to repair DNA damage at DNA replication forks (**McCabe, et al., 2006**; **Farmer, et al., 2005**; **Bryant, et al., 2005**). PARP inhibitors have been shown to have clinical efficacy in germline BRCA1/2 mutant (gBRCA1/2m) ovarian cancers and triple-negative breast cancers (TNBC) (reviewed in **Lord & Ashworth, 2017**).

Triple-negative breast cancer (TNBC), defined by the lack of expression of ER and PR, and the absence of HER2 overexpression and amplification, represents about 10-20% of all breast cancers. TNBC patients have overall worse prognosis compared with other types of breast cancer with increased likelihood of early distance recurrences and death (**Bauer, et al., 2007**). Metastatic disease is marked by a high rate of visceral and central nervous metastases with a median survival of approximately 1 year (**Kassam, et al., 2009**). Novel therapeutic strategies are therefore highly needed.

Recent advances in the biology of the disease might offer opportunities with the classification of this heterogeneous entity into molecular subtypes with distinct drivers (**Bareche, et al., 2018**), including patients with gBRCA1/2m. Indeed, two phase 3 trials that enrolled metastatic breast cancer patients with germline BRCA1 or BRCA2 mutations have reported positive results with PARP inhibitors olaparib (**Robson, et al., 2017**) and talazoparib (**Litton, et al., 2018**) versus standard chemotherapy. Following these results, the US FDA approved olaparib (Lynparza®) and talazoparib (Talzenna®) for the treatment of germline BRCA-mutated locally advanced or metastatic breast cancer.

Even though the prevalence of BRCA1 and BRCA2 mutations is higher in TNBC (up to 24% in some cohorts) (**Copson, et al., 2018**), the vast majority of patients with TNBC do not carry germline BRCA1 or BRCA2 mutations and would therefore not derive benefit from treatment with single agent PARP inhibitor therapy (**O'Shaughnessy, et al., 2014**).

3.3 Rationale and Mechanism for BET Inhibitors in BRCA1/2 wt TNBC

Although several patients with HR deficiency (HRD) benefited from treatment with PARP inhibitors, the majority of HR proficient patients did not. Therefore, strategies to induce a "BRCAness" phenotype, namely through inhibition of HR in cancer cells are actively being pursued. Recently, significant pre-clinical evidence has shown that BETi synergize with PARPi. Among 20 well-characterized epigenetic drugs targeting 7 classes of epigenetic regulators, only BET inhibitors sensitized the response of cancer cells to a PARP inhibitor (PARPi) by inducing strong synergistic effects with olaparib (**Yang, et al., 2017**) through downregulation of the transcription of several HR genes. Additional recent reports show concordant data on the synergism of PARP inhibitors and BET inhibitors in homologous recombination HR-proficient tumors, including breast cancer (**Yang, et al., 2017; Karakashev, et al., 2017; Sun, et al., 2018; Wilson, et al., 2018**). We and others hypothesize that BETi may suppress HR and enhance non-homologous end joining (NHEJ), thereby sensitizing HR-proficient cancer cells to PARP inhibition (**Wilson, et al., 2018**).

Early clinical trials with BETi showed limited single-agent activity in patients with hematologic malignancies (**Berthon, et al., 2016**), NUT carcinoma (**Stathis, et al., 2016**) and very recently in solid tumors (**Aftimos, et al., 2017**). However, there is promise for a BETi in combination with

other agents as they modulate resistance mechanisms and confer sensitivity to various agents. Several combination clinical trials are ongoing with BETi, including combination with checkpoint monoclonal antibodies, androgen receptor antagonists, estrogen modulators, BCL2 inhibitors, and others.

3.4 ZEN003694

ZEN003694 is a structurally novel, orally bioavailable small molecule that epigenetically regulates gene expression through bromodomain and extra-terminal domain (BET) inhibition. ZEN003694 is a small molecule with an empirical formula of [redacted] and a molecular weight of [redacted]. ZEN003694 was discovered and developed by Zenith Epigenetics Ltd. and has broad potential as an anti-proliferative agent in solid tumors and hematologic malignancies.

ZEN003694 and its major active metabolite, ZEN003791, bind BET bromodomains and selectively inhibit the BET family member BRD4 binding to super-enhancers in chromatin, in turn inhibiting expression of BRD4-dependent genes MYC and BCL-2 family members that drive proliferation and inhibit apoptosis of cancer cells. ZEN003694 and ZEN003791 were equipotent biochemically and in cell assays. [redacted] Based on extensive in vitro binding studies, ZEN003694 and ZEN003791 are considered to have low potential for off-target pharmacologic effects.

3.5 Talazoparib

Talazoparib is a potent, orally available small molecule PARP inhibitor in development for the treatment of a variety of human cancers. Talazoparib exerts cytotoxic effects via 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, thereby preventing DNA repair replication, and transcription (**Murai, et al., 2012**) through alternative mechanisms, resulting in higher potencies than other PARP inhibitors.

In vitro pharmacology studies with talazoparib demonstrated potent and selective inhibition of PARP1 (50% inhibitive concentration [IC50] = 0.7 nM) and PARP2 (IC50 = 0.3 nM) catalytic activity in a biochemical assay. Robust cytotoxicity following talazoparib treatment was observed in a panel of breast, prostate, pancreatic, and colorectal cancer cell lines with defects in deoxyribonucleic acid (DNA) damage repair pathways. Evaluation of PARP trapping in breast and prostate cancer cell lines treated with talazoparib resulted in increased trapping in the presence of single-strand break inducing agent methyl methane sulfonate (MMS). The reduced population growth and cytotoxicity observed in the DNA damage repair (DDR) assays are consistent with the proposed mechanisms of action for talazoparib: catalytic activity inhibition and PARP trapping.

In vivo, antitumor efficacy of single agent talazoparib was better than carboplatin in a breast cancer patient-derived xenograft (PDX) model when dosed orally once daily (QD) at 0.3 mg/kg. Breast

cancer PDX models (one each with mutated BRCA1 and mutated BRCA2, and 3 models with wild type BRCA1/2) evaluated with talazoparib dosed twice a day (BID) at 0.07 mg/kg or 0.15 mg/kg showed that talazoparib elicited the strongest, statistically significant (compared to vehicle), dose dependent tumor growth inhibition (TGI) response (100% tumor-free survival [TFS]) in the BRCA1-mutated PDX model, but also elicited statistically significant TGI responses in the BRCA2-mutated model and BRCA1/2 wild type models. While activity was most robust in the BRCA1 mutated model, talazoparib was also active in the BRCA2 mutant and in the presence of wild type BRCA1/2, possibly due to other unknown DDR-related mutations.

The absorption, distribution, metabolism and elimination of talazoparib have been characterized in mice, rats and dogs, as well as human tissues. Talazoparib was orally bioavailable with low plasma clearance and moderate volume of distribution in rats and dogs. Talazoparib was highly bound to plasma proteins in rodent and moderately bound in dog, monkey, and human plasma. Following oral administration of [14C]talazoparib to pigmented rats, drug-derived radioequivalents were widespread in most tissues including the bone marrow (BM) and were completely eliminated from all tissues by 168 h, including melanin containing tissues. In several studies, talazoparib showed negligible brain distribution in mice and rats. In vitro, talazoparib is metabolically stable in liver microsomes and hepatocytes of nonclinical species and humans. In vivo, talazoparib mainly circulates as unchanged drug in rats, dogs and humans. In rats and dogs, the majority of the [14C]talazoparib-derived radioactivity was eliminated as unchanged drug in the feces with excretion in the urine as a minor route, however, in humans [14C]talazoparib-derived radioactivity was mainly eliminated as unchanged drug in the urine, with excretion in the feces as a minor route of elimination. The nonclinical toxicologic profile of talazoparib has been characterized through the conduct of studies including repeat dose toxicity in rat and dog of ≤13-week duration, genetic toxicity (in vitro and in vivo), embryo-fetal development in rat, and phototoxicity, in accordance with the International Council for Harmonisation (ICH) S9 guidelines. Based on the cumulative evaluation of the toxicology profile of talazoparib, the primary talazoparib-related target organ findings include effects on the hematolymphopoietic system, the male reproductive system and the gastrointestinal (GI) system in both rat and dog. Additional target organ findings observed in rat only include findings in the female reproductive system and liver. Talazoparib is clastogenic in vitro in human peripheral blood lymphocytes (HPBLs), in cancer cell lines and in vivo in rat. Talazoparib caused frank fetotoxicity in an embryo-fetal development study in rat.

The primary nonclinical toxicology profile of talazoparib following oral administration can be largely explained by the pharmacological effects of talazoparib on rapidly dividing cells (talazoparib-induced PARP inhibition). Talazoparib mechanism of action (cytotoxicity) is dependent on the inhibition of PARP1/2 enzyme activity (inhibition of catalytic activity) and its robust PARP trapping ability at the site of damaged DNA (causing S-phase induced double-stranded DNA [dsDNA] break leading to apoptosis and/or necrosis). Evaluation of the cumulative toxicological profile of talazoparib suggests that the hematolymphopoietic and testes toxicities occur at subtherapeutic clinical exposure margins, while the GI, liver and ovary findings occur in rat at higher clinical exposure margins and are potentially mediated by a combination of the catalytic activity inhibition and PARP trapping activity. However, the clastogenic potential is considered to be mainly a result of talazoparib-induced inhibition of the PARP catalytic activity. The frank embryo-fetal toxicity observed in pregnant female rat in the embryo-fetal development

(EFD) study is considered to be a result of both the clastogenic and cytotoxic activities of talazoparib.

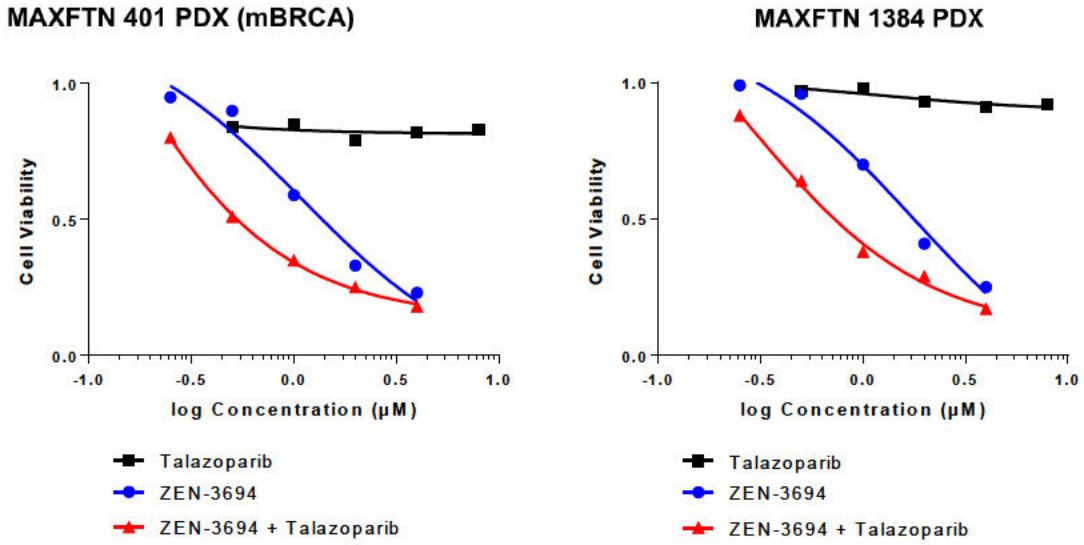
The nonclinical pharmacologic, PK and toxicologic properties of talazoparib have been thoroughly evaluated and support the use of talazoparib in advanced cancer patients.

Talazoparib has also been shown to enhance the cytotoxic effects of DNA damaging chemotherapy, including temozolomide and irinotecan, in both in vitro and in vivo preclinical models.

3.6 ZEN003694 Preclinical Data in TNBC Models

Zenith's preclinical data show [redacted] ZEN003694 synergizes with talazoparib in patient-derived TNBC models that are insensitive to talazoparib alone (**Figure 2)**. Among 9 TNBC models tested, 2 models demonstrated synergy with talazoparib (one model had a BRCA1 mutation and the second model was BRCA1/2 wild-type); whereas the remaining 7 showed additivity (**Figure 2**; synergistic data shown only). All models were sensitive to ZEN003694, but resistant to talazoparib. [redacted]

Figure 2: Synergistic combination of ZEN003694 and talazoparib in two TNBC PDX models



MAXFTN 401 is a triple-negative adenocarcinoma, stage M1, lung met, with prior radiotherapy and has a frameshift mutation in BRCA1. MAXFTN 1384 is a triple-negative adenocarcinoma, stage M1, brain met, with prior radiotherapy and with wild-type BRCA1 gene. The data show viability of spheroids quantified after 10-14 days in vitro. Both models are insensitive to talazoparib alone, whereas the addition of ZEN003694 synergizes with talazoparib to inhibit cell viability.

[redacted]

[redacted]

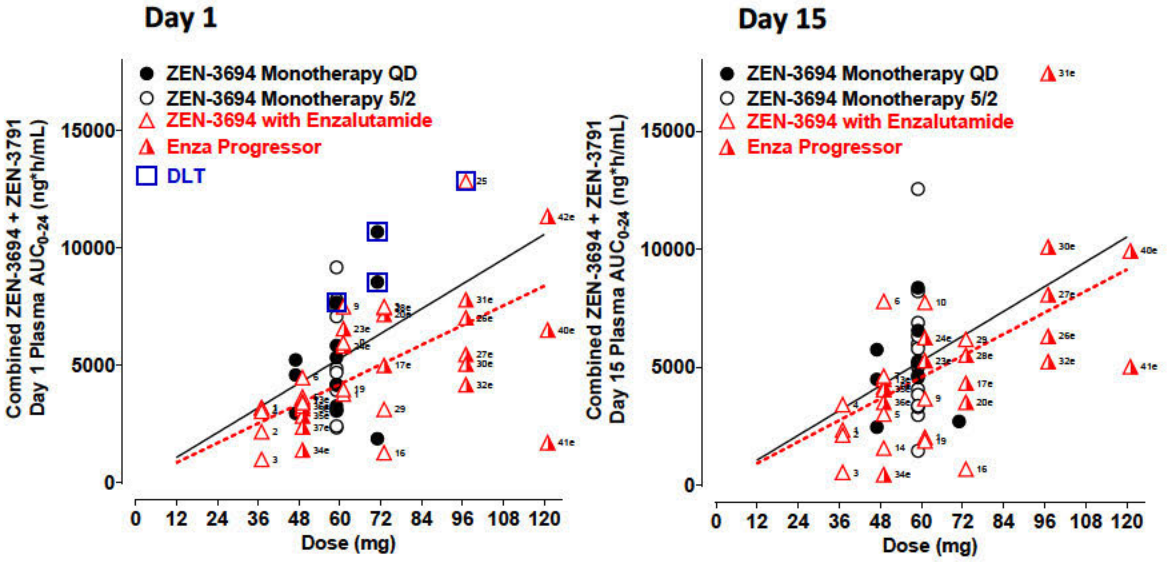
3.7 ZEN003694 Clinical Data

Clinical data to date from mCRPC trials show that ZEN003694 has dose proportional pharmacokinetics, minimal CYP liabilities, and modulates the target at safe doses. A single agent clinical study of ZEN003694 was completed in 2017 and a combination study of ZEN003694 plus enzalutamide is ongoing.

The $AUC_{0\text{-}24h}$ versus dose for day 1 and day 15 displayed in **Figure 4** show dose proportionality and minimal interaction with enzalutamide. As ZEN003694 has an active metabolite with very similar properties as ZEN003791, the graphs show combined $AUC_{0\text{-}24h}$. The data with a blue rectangle highlight the exposure of the patients who experienced a DLT in cycle 1 (28 days) of dosing. The MTD of ZEN003694 was 60mg QD in the single agent study but 96mg QD in the combination study was tolerated with one DLT out of six patients. Dosing at 120mg QD has also been tolerated by a cohort of three patients in the combination study and three additional patients

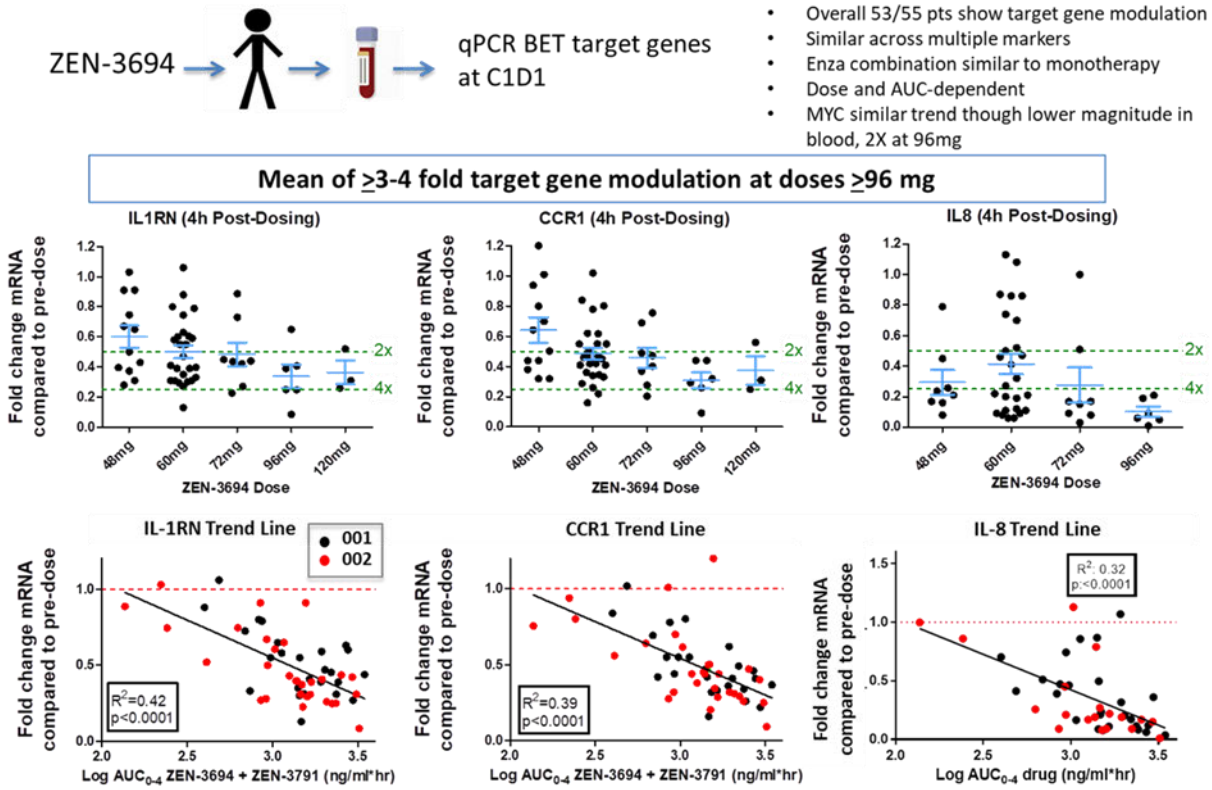
are to be tested at this dose. All of the DLTs to date are related to gastrointestinal toxicity including nausea, dehydration, vomiting and decreased appetite. Gastrointestinal (GI) toxicity is an on-target effect of BET inhibition on GI stem cells. The higher MTD in the combination study is potentially due to better management of GI toxicities with the implementation of PRN use of antiemetics upon onset of nausea and recommendation of oral hydration in the combination study; outlier high exposures of two patients who experienced a DLT in the single agent study; or higher metabolite (ZEN003791) to parent (ZEN003694) ratio in the combination study (data not shown). [redacted]

Figure 4: AUC0-24h versus dose for ZEN003694 + ZEN003791



Target modulation data is shown in **Figure 5** based on a gene expression whole blood assay (**Tsujikawa, et al., 2017**). The data show that the target is moderately modulated approximately 2x at 48 mg and > 4x at 96 mg and 120 mg.

Figure 5: Target modulation by ZEN003694



Dose-dependent modulation of IL1RN, CCR1, and IL-8 in the whole blood of CRPC patients in the ZEN003694-001 and ZEN003694-002 clinical trials.

Clinical data from both mCRPC studies have identified the following adverse drug reactions (drug related and occurring in > 2 patients) (**Table 2** and **Table 3**); visual disturbance (typically a transitory perception of brighter lights and/or light flashes, with or without visual color tinges, and with no functional consequences), nausea, fatigue, decreased appetite, vomiting, creatinine increase, platelet decrease, diarrhea, dehydration, decreased weight, dizziness, dysgeusia, and thrombocytopenia. These ZEN003694-related adverse events (AEs) were generally Grade 1 or 2 in severity, were managed clinically, did not result in long-term sequelae, and resolved in the absence of drug exposure.

The most frequent and/or clinically important AEs (GI symptoms such as nausea, vomiting, diarrhea, and constipation in 59% of patients, visual disturbance in 61% of patients, and thrombocytopenia in 7% of patients) can be related to the mechanism of action and molecular pharmacology of ZEN003694, and thus appear to be dose-related and readily reversible; they may also be managed through modulation of exposure (e.g., changing the dosing regimen or withdrawing the drug). GI symptoms have also been managed through the use of anti-emetics and proactive attention to nutrition and hydration; constitutional symptoms generally respond to dose reduction or short-term dose holds. Adverse events to date have been transitory, reversible, and manageable with symptomatic therapy.

Table 2: Grade 1-4 adverse events in mCRPC single agent study (only shown for AEs in ≥ 2 patients)

	48mg QD n=4*	60mg QD n=5**	60mg (5/2) n=15**	72mg QD n=2*	TOTAL n=26
Abdominal pain			2		2
Appetite decreased	1	3	2	2	8
Constipation	1	1			2
Creatinine Increased	2	1		2	5
Dehydration	1	1		2	4
Diarrhea	1	1	1	1	4
Dizziness			1	1	2
Dysgeusia			2		2
Fatigue	2	4	6	1	13
Myalgia		1	1		2
Nasal Congestion		1	1		2
Nausea	2	5	8	1	16
Platelets decreased	1		2		3
Rash	1		1		2
Thrombocytopenia	1	1	1		3
Visual disturbance	3	3	12	1	19
Vomiting	1	3	1	1	6
Weight loss		1	2		3

* One patient enrolled in the 72mg QD cohort was switched to 48mg QD in Cycle 1 (C1)
** One patient on 60mg QD was switched to 5/2 in C1 and is reported with the 5/2 cohort

Table 3: Grade 1-4 adverse events in mCRPC combination study (only shown for AEs in ≥ 2 patients)

	36mg QD n=4	48mg QD n=17	60mg QD n=6	72mg QD n=6	96mg QD n=15	120mg QD n=4	TOTAL n=52
Appetite decreased		2	2	1	4	3	12
Constipation		1			1		2
Creatinine increased			2		2		4
Dizziness	1			1	1		3
Dysgeusia		1	1	1	4	1	8
Fatigue	1	7	1	2	2	3	16
Flatulence		2					2
Glucosuria					2		2
Hypophosphatemia			1	1			2
Nasal congestion					3		3
Nausea		5	2	4	5	3	19
Platelets decreased		1	1	3	1		6
Rash, maculopapular		1			1		2
Visual disturbance	3	10	5	5	9	4	36
Vomiting		1				1	2
Weight loss	1			1	1	1	4

Summary of Grade 3/4 adverse events are shown in **Table 4**. The data show that the main Grade 3/4 AEs are related to GI toxicity in the single agent and in the combination mCRPC study. The hypokalemia and hypophosphatemia are manageable by oral administration of potassium and phosphate, respectively. The GFR decrease was in a patient that previously had his kidney resected due to renal cell carcinoma.

Table 4. Grade 3/4 related adverse events in both single agent and combination Phase 1 mCRPC trials

	Single Agent					Combination					
	48mg QD n=4	60mg QD n=5	60mg (5/2) n=15	72mg QD N=2		36mg QD n=4	48mg QD n=11	60mg QD n=6	72mg QD n=6	96mg QD n=8	120mg QD n=4
GRADE	3 (4)	3 (4)	3 (4)	3 (4)		3 (4)	3 (4)	3 (4)	3 (4)	3 (4)	3 (4)
Appetite ↓		1*									
Dehydration		1		2*						1	
Fatigue		1*		1*			1				
GFR ↓										1	
Hypokalemia									1		
Hypophosphatemia								1	1		
Serum Amylase ↑				1							
Thrombocytopenia			(1)								
Nausea		1								1*	
Vomiting				1*							

* DLT events

3.8 Talazoparib Clinical Data

A summary of talazoparib clinical data is presented below. A comprehensive review of talazoparib may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB). Investigators are to review this document prior to initiating this study.

Investigations of talazoparib are currently on-going with talazoparib being evaluated, both as single agent or in combination, in mCRPC, early triple-negative breast cancer, ovarian cancer, and small cell lung cancer.

3.8.1 Pharmacokinetics

The PK of talazoparib as a single agent has been evaluated in a total of 7 clinical studies. The PK of talazoparib was similar in patients with hematological malignancies and patients with solid tumors, and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. A food-effect study showed that food had no clinically meaningful effect on the extent of absorption; talazoparib can be administered without regard to food. The plasma exposure of talazoparib is dose proportional in the dose range of 0.025 mg to 2 mg QD, suggesting linear PK. The mean terminal half-life (t½) was approximately 4 days. Talazoparib accumulated after 1 mg QD dosing with a median accumulation ratio (Rac) ranging from 2.33 to 5.15, consistent with its t½. Steady state was reached around 3 weeks after the start of talazoparib dosing. Talazoparib undergoes minimal hepatic metabolism in humans. Renal excretion of unchanged talazoparib was the major elimination pathway of talazoparib. Talazoparib is moderately bound to human plasma proteins (74%, in vitro) and is evenly distributed across human blood cells and plasma compartments. In vitro, talazoparib did not significantly interact with any of the major cytochrome P450 (CYP) or uridine 5'-diphospho-glucuronosyltransferase (UGT) drug metabolizing enzymes, nor was it an inhibitor of any ATP-binding cassette (ABC) or solute carrier (SLC) drug. Talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase or decrease when coadministered with P-gp or BCRP inhibitors or inducers, respectively. Based on the high oral bioavailability observed in rats, dogs, and humans, absorption of talazoparib is not limited by these efflux transporters.

Additional ongoing Phase 1 company-sponsored clinical studies are evaluating the PK of talazoparib in patients with renal impairment or hepatic impairment, and DDIs of talazoparib with itraconazole and rifampin.

3.8.2 Safety

A total of 502 patients with solid tumors received 1 mg/day talazoparib through 31 January 2018 in 5 Sponsor-initiated studies, namely Study 673-301 (phase 3 EMBRACA pivotal, open-label randomized 2-Arm, Multicenter Study of Talazoparib [BMN 673] Versus Physician's Choice in Patients With Germline BRCA Mutations and Locally Advanced and/or Metastatic Breast Cancer Who Had Prior Chemotherapy for Metastatic Disease study), Study 673-201 (phase 2 ABRAZO open-label non randomized study in Patients With Germline BRCA Mutations and Locally

Advanced and/or Metastatic Breast Cancer), Study MDV3800-13 (open label extension study), Study PRP-001 (Phase 1 dose escalation study in patients with advanced or recurrent solid tumors), and Study MDV3800-14 (Phase 1 Study MDV3800-14: cardiac repolarization study in patients with advanced solid tumors).

The most common adverse events (≥20%) related to talazoparib 1 mg/day, mostly with grade 1 or 2 severity, were anemia (45.8%), fatigue (36.1%), nausea (32.5%), neutropenia (21.9%), and alopecia (20.1%). Grade 3 or 4 drug-related adverse events occurring in ≥5% of patients were related to myelosuppression, namely anemia (34.1%), neutropenia (13.9%), thrombocytopenia (10.6%), and platelet count decreased (5.4%). Most common serious adverse events (≥3 patients) considered related to talazoparib were anemia (4.6%), thrombocytopenia/platelet count decreased (2.4%), and neutropenia (0.6%).

A total of 23 of 502 patients had an adverse event that led to death, of these, only veno-occlusive liver disease occurred in a patient was assessed as related to study drug by the investigator.
Adverse events leading to treatment discontinuation occurred in 4% of patients receiving talazoparib 1 mg/day, the most common being anemia (in 3 patients) and increased alanine aminotransferase (ALT, in 2 patients). Among the 502 patients in the talazoparib 1 mg/day patient population, 63.9% had adverse events that led to dose reduction and 61.2% had a TEAE that led to dosing interruption, most commonly associated with myelosuppression.

In general, the adverse events associated with talazoparib are detectable through routine laboratory and clinical monitoring and may be managed with supportive care or dose reductions or interruptions.

3.8.3 Efficacy

Efficacy data have been obtained from 3 Sponsor-initiated studies (PRP-001, Studies 673-201, and 673-301) evaluating talazoparib in patients with advanced or metastatic breast cancer.

In the Phase 1 first-in-human study (Study PRP-001 [C3441007]) in patients with advanced or recurrent solid tumors, a total of 110 patients were treated at a range of talazoparib doses (0.025-1.1 mg/day). Data from this study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma.

In an open-label Phase 2 study (Study 673-201, [C3441008, ABRAZO]) of talazoparib in patients with germline BRCA-mutated locally advanced or metastatic breast cancer, 83 patients were treated with talazoparib 1 mg/day across 2 cohorts. Cohort 1 enrolled 49 patients (48 treated) who had a partial response (PR) or complete response (CR) to a prior platinum-containing regimen for metastatic disease with disease progression >8 weeks following the last dose of platinum. Cohort 2 enrolled 35 patients who received 3 or more prior chemotherapy regimens and no prior platinum therapy for metastatic disease. Cohort 1 had an objective response rate (ORR) of 20.8% (95% CI: 10.5, 35.0) including 2 CRs (4.2%). Cohort 2 had an ORR of 37.1% (95% CI: 21.5, 55.1). Median duration of response (DOR) was 4.9 months (interquartile range [IQR]: 2.8, 7.1) in Cohort 1 and 4.2 months (IQR: 3.2, 5.6) in Cohort 2 (**Turner, et al., 2017**).

In the pivotal randomized Phase 3 study (Study 673-301, [C3441009, EMBRACA]) of talazoparib versus physician's choice treatment (PCT) in patients with germline BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, 431 patients overall were randomized in a 2:1 ratio to receive talazoparib 1 mg/day (n = 287) or 1 of 4 PCTs (n = 144). In this study, talazoparib demonstrated significantly prolonged progression-free survival (PFS) by blinded independent central review (BICR) assessment when compared to PCT. Median PFS by BICR in the talazoparib arm was 8.6 months (95% CI: 7.2, 9.3) compared to 5.6 months (95% CI: 4.2, 6.7) in the PCT arm (**Litton, et al., 2018**).

3.9 Study Rationale

The vast majority of patients with TNBC do not carry germline BRCA1 or BRCA2 mutations and would therefore not derive benefit from treatment with single agent PARP inhibitor therapy Therefore, strategies to induce a "BRCAness" phenotype, namely through inhibition of HR in cancer cells is needed. Recently, significant pre-clinical evidence has shown that BETi synergize with PARPi through downregulation of the transcription of several HR genes. We and others hypothesize that BETi may suppress HR and enhance non-homologous end joining (NHEJ), thereby sensitizing HR-proficient cancer cells to PARP inhibition (**Wilson, et al., 2018**).

To test this hypothesis, we propose this Phase 2 trial with the combination of talazoparib and ZEN003694 in previously treated metastatic/advanced BRCA1/2 -proficient TNBC. Talazoparib is a potent and selective inhibitor of PARP. In addition to inhibiting PARP catalytic activity, talazoparib traps PARP-DNA at sites of single-agent DNA breaks (**Murai, et al., 2014**). ZEN003694 is s a potent and selective inhibitor of the BET family of proteins and is currently being tested in a Phase1b/2a mCRPC clinical trial. Clinical data to date show that ZEN003694 has dose proportional pharmacokinetics, minimal CYP liabilities, and modulates the target at safe doses. Based on ZEN003694 safety profile as described in Section **3.7**, ZEN003694 is expected to combine well with talazoparib.

The first part of this study is dose escalation using a 3x3 design to determine a safe and optimal dose of ZEN003694 when given in combination with talazoparib. The second part of the study is a Simon two-stage design to determine overall response rate to the combination of ZEN003694 and talazoparib.

3.10 Dosing Rationale

Based on the safety and PK/PD data from the ZEN003694 mCRPC trials, a reasonable ZEN003694 dose to initiate in this combination trial of ZEN003694 plus talazoparib is 48 mg QD for ZEN003694 in combination with 1 mg QD talazoparib. The MTD of ZEN003694 was 60 mg QD in the single agent study but the dose of 96 mg QD in the mCRPC combination study was tolerated with one DLT out of six patients. Dosing at 120 mg QD has also been tolerated by a cohort of three patients in this ongoing combination study of ZEN003694 plus enzalutamide in mCRPC patients. The reason for the higher MTD in the this mCRPC combination study is not definitively known but may relate to one or more factors, including: proactive management of GI toxicities with the implementation of PRN use of antiemetics upon onset of nausea and the recommendation of oral hydration in the combination study; outlier high exposures of the two patients who experienced a DLT in the single agent study; and/or the higher ratio of active metabolite to parent

in the mCRPC combination study with enzalutamide. Although talazoparib is not a CYP3A4 inducer and is not expected to induce a higher ratio of the ZEN003694 active metabolite to parent in this TNBC combination study, it is expected that 48 mg of ZEN003694 will be tolerated in combination with 1 mg talazoparib. In case of clinically significant AEs, a dose reduction and dose hold schema is described in Section **8**. Proactive management of nutrition, hydration, and anti-emetics will also be implemented in this trial, and pharmacokinetic monitoring will allow management of systemic exposure within known tolerated levels.

3.11 Rationale for Expanding Phase 2 Study and Patient Pre-Selection

Data from Dose Escalation and Simon 2-Stage

The study enrollment for the dose escalation and Simon 2-stage parts of the study has been completed and 57 patients have been dosed. Dosing was started at 48 mg oral daily (QD) for ZEN003694 plus 1 mg QD talazoparib. Dose limiting toxicity (DLT) of grade 4 thrombocytopenia was seen in 2 patients. Two additional dosing cohorts were tested (48 mg QD ZEN003694 plus 0.75 mg QD talazoparib and 36 mg QD ZEN003694 plus 1 mg QD talazoparib). Based on additional data and no reported DLTs, 48 mg QD ZEN003694 plus 0.75 mg QD talazoparib was selected as the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D) for the phase 2 portion of the study due to higher exposure and pharmacodynamic activity (low target engagement at 36 mg ZEN003694). Of the 50 evaluable patients receiving the RP2D of the combination, 11 (22%) had a confirmed objective response rate (ORR) with a median duration of response rate (DOR) of 24 weeks and this was driven by the population whose tumors were triple negative at diagnosis and did not convert from hormone receptor positive to triple negative. The most commonly reported ZEN003694-related AEs (occurring in ≥15% of patients) were thrombocytopenia, visual symptoms, fatigue, nausea, vomiting, dysgeusia, increased AST/ALT, anorexia and anemia. All AEs were reversible upon dose hold.

A development and registration plan was discussed with the FDA for extending the current study by adding additional post TROP2-ADC patients to generate statistically significant ORR and DOR data for potential accelerated approval with a commitment for a Phase 3 confirmatory trial. FDA agreed that an ORR that is significantly superior to available therapies could be used as a basis for approval. Currently, only available therapies for third line mTNBC patients who have received prior Sacituzumab-govitecan is chemotherapy which has an ORR of ~ 5-12%. The expansion with an additional 80 evaluable patients is powered to show and ORR with a lower 95% confidence interval that excludes an ORR of 20%. FDA also asked for a cohort of 10 patients to evaluate the efficacy of single agent ZEN003694. This cohort of patients will be crossed over to the combination of ZEN003694 plus talazoparib upon progression.

[redacted]

[redacted]

[redacted]

4. OBJECTIVES

4.1 Primary

Part 1

- To determine the safety, tolerability, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic triple-negative breast cancer (TNBC)

Part 2

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC

Expansion

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative at the time of initial breast cancer diagnosis and who have received TROP2-ADC in the unresectable locally advanced or metastatic disease setting.

4.2 Secondary

Part 1

- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791 and talazoparib
- To evaluate the effects of ZEN003694 and talazoparib on mRNA expression of pharmacodynamic markers
- To evaluate the clinical activity of ZEN003694 in combination with talazoparib by radiographic response rate and progression-free survival
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

Part 2

- To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib
- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

Expansion

- To evaluate the efficacy of ZEN003694 in combination with talazoparib in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative (<5%) at the time of initial breast cancer diagnosis and who have not received TROP2-ADC in the locally advanced or metastatic disease setting
- To evaluate the ZEN003694 monotherapy in patients with locally advanced or metastatic TNBC whose cancer was hormone receptor negative at the time of initial breast cancer diagnosis and who may or may not have received prior TROP2-ADC.
- To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib
- To determine the pharmacokinetics (PK) of ZEN003694, its metabolite, ZEN003791, and talazoparib
- To determine the effect of ZEN003694 and talazoparib on patient reported health status and quality of life

4.3 Exploratory

Parts 1 and 2, Expansion

- [redacted]

5. STUDY DESIGN

5.1 Part 1: Dose escalation

Part 1 is an open label, non-randomized, dose escalation of ZEN003694 in combination with talazoparib in patients with TNBC. A standard 3+3 cohort design will be utilized. Cohorts of 3 patients and up to 6 patients will be enrolled at each dose level, and each patient will participate in only one cohort. Each cycle will be 28 days in duration. Patients at each dose level will be treated and observed through the end of the first 28-day cycle before treatment of patients at the next higher dose level can begin.

Dose escalation will continue after all patients enrolled within a cohort have completed the 28-day Cycle 1 DLT observation period with either 0 of 3 patients, or no more than 1 out of 6 patients in a cohort experiencing a DLT. Dose escalation decisions will be made based on clinical safety and (when available) PK data (maximum or peak concentration [C_{max}] and area under the curve [AUC]) after review by the Investigators and the Zenith Medical Monitor. If a DLT is observed in 1 of 3 patients in a cohort, 3 additional patients will be enrolled into that cohort. If 1 of 6 patients in a cohort experiences a DLT, then dose escalation may continue in the next cohort or the MTD of the combination can be declared. If ≥ 2 of 3 – 6 patients experience DLTs within a cohort, then the MTD will be considered to have been exceeded and further dose escalation will cease. In this case, if fewer than 6 patients have been enrolled at the previous dose level, that cohort will be expanded to 6 patients to confirm the MTD. Should the MTD of the combination be exceeded at Dose Level 1, a cohort may be explored with a reduced dose of ZEN003694 or talazoparib. Cohort management is summarized below.

Number of Patients with Dose-limiting Toxicity	Action
0 of 3 or 1 of 6	Dose escalate to next cohort
1 of 3	Add 3 more patients
1 of 6	Proceed to next dose level
≥ 2 of 3 or ≥ 2 of 6	Add 3 more patients in the next lower dose level if only 3 patients were treated in the next lower dose. If 6 patients were treated at the next lower dose level and no more than one patient had DLT, then the next lower dose is the MTD.

Enrollment in the dose escalation part of the study will commence with a 48 mg oral once daily dose as the starting dose for ZEN003694 in combination with a 1 mg oral once daily dose of talazoparib. The dose of ZEN003694 will be held constant throughout Cycle 1, however doses may be held for the management of toxicity. The dose of talazoparib may be held and reduced from the initial 1.0 mg dose in 0.25 mg increments in accordance with the talazoparib label and by agreement with Zenith. Dose escalation/de-escalation of ZEN003694 will proceed per the schema in **Table 5** unless intervening toxicity is observed. Alternative dosing schedules may be evaluated based on the evaluation of clinical safety and upon agreement of the Investigators and Zenith.

Alternative dosing schedules may include intermittent dosing that could necessitate a change in the cycle duration from 28 days to 21 days.

Table 5: Dose Escalation Scheme

Dose Level	ZEN003694 (mg) *	Fold Increase from Prior Dose Level
-1	36	0.75
1	48	--
2	72	1.50
* Dose de-escalation from 48 mg is allowed and additional dose levels may be explored based on safety and at the discretion of the Sponsor with agreement from the Investigators		

No intra-patient dose escalation is allowed during the first two cycles of therapy. If a patient has not experienced any Grade 2 or higher drug-related AEs after three cycles, dose escalation up to the highest ZEN003694 dose currently declared tolerable will be allowed and further intra-patient dose escalation(s) will be determined on a cycle-by-cycle basis at the discretion of the Investigators and with approval by the Sponsor.

5.1.1 Dose Escalation Safety Reviews

ZEN003694-related adverse events (AEs) for determination of DLTs will be assessed for each patient during the 28 days of Cycle 1. Teleconferences between the Sponsor and the Investigators will be held during the dose escalation phase to discuss any suspected DLTs that have occurred in patients within each cohort. The frequency of the teleconference calls will be determined by the rate of enrollment, data review, frequency of DLT notifications, discussions with investigational sites and other factors. Approximately one week after the last patient in a dose cohort completes Cycle 1 and prior to enrolling patients in the next dose, the Sponsor and Investigators will review toxicities and available PK (e.g., C_{max} and AUC) from the current cohort of the study during a teleconference call.

5.1.2 Definition of Dose-limiting Toxicity

Determination of DLT will be made during the first 28 days of treatment (i.e., Cycle 1) in the dose escalation phase. Toxicity will be graded and recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 (see **Appendix 2**). A DLT is defined as a clinically significant AE or laboratory abnormality that is considered possibly, probably or definitely related to study drug and which meets any of the following criteria:

- Grade 3 or greater non-hematologic clinical toxicity with the exception of a) Grade 3 nausea or Grade 3/4 vomiting and diarrhea unless persisting more than 72 hours despite maximal medical therapy and b) Grade 3 or 4 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis
- Grade 3 or greater fatigue for at least 1 week
- Grade 4 anemia
- Grade 4 neutropenia lasting more than 5 days

- Grade 3 or greater febrile neutropenia (temperature ≥ 38.5ºC)
- Grade 4 thrombocytopenia; or Grade 3 thrombocytopenia with clinically significant bleeding; or any requirement for platelet transfusion
- Grade 3 or 4 electrolyte abnormality lasting more than 72 hours, unless the patient has clinical symptoms, in which case all Grade 3 or 4 electrolyte abnormalities regardless of duration will be considered a DLT
- Any other Grade 3 or 4 laboratory abnormality that requires hospitalization
- An ALT or AST ≥3x ULN with concomitant total bilirubin > 2x ULN, and serum alkaline phosphatase ≤ 2x ULN (Hy's Law) For patients with hepatic metastases, AST or ALT >8x ULN or AST or ALT >5x ULN for ≥14 days
- Any Grade 3 or 4 visual symptoms
- Any toxicity that results in more than 25% of missed doses during Cycle 1 of the 28 days of treatment, with the exception of a dose hold for Grade 3 thrombocytopenia, in which case a dose hold of both talazoparib and ZEN003694 for 10 consecutive days in Cycle 1 will be allowed and not considered a DLT. For an intermittent schedule of 2-weeks on/1-week off, if any toxicity results in more than 2 missed doses during the 2-week treatment period the toxicity would be considered a DLT.
- In the situation where toxicity requires withholding study drug following the receipt of at least 75% of scheduled dosing during Cycle 1: Failure to begin Cycle 2 within 1 week of the scheduled start date due to ongoing toxicity

All patients experiencing a DLT must discontinue dosing with ZEN003694 and talazoparib, except in the event that the DLT is thrombocytopenia, in which case patients may be re-challenged with ZEN003694 and talazoparib at doses agreed upon with the Sponsor if platelets recover to at least 75,000/μL within a 10-day dose hold. All patients who discontinue treatment must complete the Safety Follow-up visit prior to discontinuation from the study.

Determination of evaluability will be made during the first 28 days of study treatment (i.e., Cycle 1) in the dose escalation phase. Patients who miss more than 25% of ZEN003694 or talazoparib doses (except in the case of a dose hold for thrombocytopenia where 10 consecutive days of missed doses are allowed); or fail to begin Cycle 2 within 1 week of the scheduled start date for reasons other than drug-related toxicity will be considered unevaluable and will be replaced.

5.1.3 Definition of the Maximum Tolerated Dose

The MTD is defined as the highest dose level of ZEN003694 in combination with talazoparib at which no more than 1 of 6 patients experiences a DLT during the first cycle of therapy.

5.1.4 Definition of the Recommended Phase 2 Dose

The RP2D as determined in Part 1 of the study is defined as the dose level of ZEN003694 in combination with talazoparib recommended for further clinical study. The RP2D may be the

same as the MTD or modified from the MTD based on assessments of overall exposure, safety experience in Cycle 2 and beyond, PD and clinical benefit data in this study. Part 2: Simon 2-Stage

Once an RP2D of ZEN003694 in combination with talazoparib has been determined in the dose escalation part of the study, 17 patients will be enrolled in Stage 1 of a Simon 2-Stage design (**Simon, 1989**) for evaluation of objective response (complete response (CR), partial response (PR), or stable disease (SD) for ≥ 4 cycles) by RECIST 1.1 (**Eisenhauer, 2009**). If there are ≥4 objective responses the study will proceed to Stage 2. If there are <4 responses, the study will be stopped.

If at least 4 patients in Stage 1 have an objective response (CR, PR or SD for ≥ 4 cycles) by RECIST 1.1, 20 patients will be enrolled in Stage 2 of the Simon 2-Stage design. Patients will receive daily RP2D doses of ZEN003694 in combination with 1 mg talazoparib. Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study.

5.2 Expansion

The expansion of the study will be implemented under amendment following the determination of the RP2D of ZEN003694 in Part 1 and after meeting the primary endpoint of clinical benefit rate of 35% in Part 2. The study will be expanded to enroll an additional 120 patients with locally advanced or metastatic TNBC that is without germline BRCA1/BRCA2 mutations and was hormone receptor negative (<5%) at the time of initial breast cancer diagnosis.

Expansion Cohort A: Combination Treatment in post-TROP2-ADC patients: Eighty (80) patients who have received prior TROP2-ADC treatment will receive daily RP2D doses of ZEN003694 (48mg QD) in combination with talazoparib (0.75mg QD). Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from the study.

Expansion Cohort B: ZEN003694 Monotherapy: As mandated by the FDA to assess any potential single agent ZEN003694 activity, ten (10) patients will initially receive daily doses of 48mg ZEN003694 as monotherapy with the option to cross-over to combination treatment of 48mg ZEN003694 plus 0.75mg talazoparib at the time of disease progression (but no sooner than after 6 weeks of monotherapy). Patients in the cross-over group may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from study.

Expansion Cohort C: Combination Treatment in TROP2-ADC-naïve patients: Thirty (30) patients who have not received prior TROP2-ADC will receive daily RP2D doses of ZEN003694 (48mg QD) in combination with talazoparib (0.75mg QD). Patients may continue receiving ZEN003694 in combination with talazoparib until radiographic or clinical progression, unacceptable toxicity, requirement for non-protocol therapy or patient withdrawal from the study.

5.3 Number Patients and Sites

In Parts 1 and 2, up to 52 evaluable patients will be enrolled in the study at approximately 10 sites (in the US and Western Europe). Approximately 15 patients will be enrolled in Part 1 (dose escalation) and approximately 37 patients will be enrolled in the Part 2 of the study with 17 patients enrolled in Stage 1 of the Simon 2-Stage design and 20 patients enrolled in Stage 2.

In the Expansion phase, approximately 120 evaluable patients will be enrolled in the study (80 patients in Cohort A; 10 patients in Cohort B; and 30 patients in Cohort C) at approximately 18 sites (approximately 9 sites in the US; 4 sites in Western Europe; and 5 sites in China). Cohort A and B will enroll at all US and EU sites. Cohort C will be enrolled at sites in China only.

5.4 Study Duration

The duration of Stage 1 is approximately 6 months to enroll 17 patients who are treated through 5 cycles (2 post baseline scans). The duration for Stage 2 is approximately 12 months to enroll 20 patients who are treated through 5 cycles (2 post baseline scans).

The duration of the Expansion phase is approximately 24 months.

5.5 Premature Study Termination or Suspension of Enrollment

The Sponsors have the right to terminate the participation of an individual study site or the entire study, at any time, for any reason. Reasons for terminating the study include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data records are inaccurate or incomplete
- The Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation or development of ZEN003694

In addition, the Sponsor may suspend enrollment in the study at any time for any reason.

All Investigators and appropriate Regulatory Authorities will be promptly notified upon early termination of the study. In addition, Investigators and Regulatory Authorities will be promptly notified if enrollment is terminated or suspended for any reason.

6. PATIENT SELECTION

6.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for the study:

1. Females or males age ≥ 18 years (at time of signing informed consent)
2. **Parts 1 and 2 only:** Histologically confirmed metastatic or recurrent or locally advanced triple-negative breast cancer (estrogen receptor (ER) ≤10%; progesterone receptor (PR) ≤10%; and HER2 negative by immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH)

   Expansion only: Histologically confirmed metastatic or recurrent, or locally advanced triple-negative breast cancer as defined by the most recent American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.
3. Patient is not a candidate for endocrine based therapy, based on Investigator judgement
4. Have a history of progressive disease despite prior therapy
5. **Part 1:** Have had at least 1 prior cytotoxic chemotherapy

   Part 2: Have had no more than 2 prior chemotherapy-inclusive regimens for locally advanced or metastatic disease, unless approved by the Sponsor (no limit on prior targeted anticancer therapies such as mechanistic target or rapamycin (mTOR) or CDK4/6 inhibitors, immune-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or VEGF.)

   Expansion Cohort A (combination treatment in post-TROP2-ADC patients): Have received TROP2-ADC therapy for unresectable locally advanced or metastatic disease.

   Expansion Cohort B (ZEN003694 monotherapy): Have had at least 1 prior systemic therapy for locally advanced or metastatic disease which may or may not have included a TROP2-ADC.

   Expansion Cohort C (combination treatment in TROP2-ADC-naive patients): Have had at least 1 prior systemic therapy for locally advanced or metastatic disease and who have not received prior TROP2-ADC therapy.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. **Part 2 and Expansion only:** Measurable disease per RECIST version 1.1
8. Adequate laboratory parameters at Screening including:
   a. **Parts 1 and 2:** Hemoglobin ≥ 10.0 g/dL without transfusions during the 4 weeks prior to Screening. **Expansion:** Hemoglobin ≥ 9.0 g/dL
   b. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   c. Platelet count ≥ 150,00/mm^3

d. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.0 x ULN or if liver function abnormalities due to liver metastases AST and ALT ≤ 5.0 x ULN

e. Total bilirubin ≤ 1.5 x ULN (≤ 3.0 x ULN for subjects with known Gilbert's syndrome)

f. Calculated (Cockcroft-Gault formula) or measured creatinine clearance ≥ 60 mL/min

g. Prothrombin time (PT), international normalized ratio (INR) and partial thromboplastin time (PTT) < 1.5 x ULN

9. Female subjects may be enrolled if they are not of childbearing potential, permanently sterile or who are post-menopausal defined as no menses for at least 1 year without an alternative medical cause and FSH levels in the post-menopausal range. Female subjects of childbearing potential may be enrolled if they consistently and correctly use a highly effective form of contraception from the time point of study drug administration until at least 7 months thereafter. Highly effective forms of contraception include: combined (estrogen and progestogen hormonal contraceptives (oral, intravaginal, transdermal) associated with inhibition of ovulation; progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence. Female subjects should not donate eggs from the time point of study drug administration until at least 7 months thereafter.

10. Males with partners of childbearing potential may be enrolled if they use a condom when having sex with a pregnant woman or with a non-pregnant female of childbearing potential from 21 days before the first dose of study drug through 4 months after the last dose of study drug, and males should not donate sperm from the time point of study drug administration until at least 4 months thereafter. Contraception should be considered for a non-pregnant female partner of childbearing potential.

11. Females of childbearing potential must have a negative serum or urine pregnancy test before the first dose of study drugs and must agree to pregnancy tests during the study.

12. Females may not be breast-feeding at the first dose of study drugs, during study participation or through 7 months after the last dose of study drugs

13. Ability to swallow capsules and comply with study procedures

14. Ability to understand and willingness to sign informed consent form prior to initiation of any study procedures

6.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Documented germline mutations of BRCA1 or BRCA2

2. **Parts 1 and 2 only**: Evidence of disease progression during platinum treatment either in the neoadjuvant or in the metastatic setting. For patients receiving platinum in the neoadjuvant setting, at least 6 months must have elapsed between the last dose of platinum-based treatment and enrollment

3. **Part 2 only:** Patients with inflammatory breast cancer

4. Current or anticipated use of medications known to be strong inhibitors or inducers of CYP3A4 or substrates of CYP1A2 with narrow therapeutic windows. Strong inhibitors, inducers or substrates must be discontinued at least 7 days prior to the first administration of study drug.

5. Current or anticipated use within 7 days prior to the first administration of study drug, or during the study, of strong P-gp inhibitors.

6. Use of oral Factor Xa inhibitors (i.e., rivaroxaban, apixaban, betrixaban, edoxaban otamixaban, letaxaban, eribaxaban) and Factor IIa inhibitors (i.e., dabigatran). Low molecular weight heparin is allowed

7. Prior anticancer therapy (chemotherapy, radiation, hormone therapy, immunotherapy or investigational agent) within 3 weeks from the start of study drug (except for nitrosoureas and mitomycin C within 6 weeks from start of study drug)

8. **Parts 1 and 2 only:** Radiation to >25% of the bone marrow

9. Treatment with a bone-targeted radionuclide within 6 weeks of first dose of study drug

10. Have previously received an investigational BET inhibitor (including previous participation in studies with the Sponsor's drug, ZEN003694); except for patients in Expansion Cohort B who received ZEN003694 monotherapy and are eligible to cross-over to combination treatment

11. Prior treatment with a PARP inhibitor

12. QTcF interval > 470 msec

13. Insufficient recovery (i.e., has not recovered to at least Grade 1) from prior treatment-related toxicities except for alopecia, fatigue and Grade 2 neuropathy

14. Non-healing wound, ulcer or bone fracture (not including a pathological bone fracture caused by a pre-existing pathological bone lesion)

15. **Parts 1 and 2 only:** Brain metastases not adequately treated and clinically stable (at the discretion of the Investigator) for at least 3 months prior to the start of study treatment, unless a shorter interval is approved by the Sponsor's Medical Monitor

    Expansion only: Progressive, symptomatic, or untreated brain metastases. CNS metastases treated definitively with surgery and/or radiation must be radiographically

stable based on imaging at least 3 months after definitive treatment. CNS metastases requiring steroid doses equivalent to prednisone doses >10 mg daily or an increase in steroid doses due to CNS disease prior to consent are not eligible

16. **Expansion only:** Disease initially diagnosed with expression of estrogen receptor (ER) or progesterone receptor (PR) as ⩾5%

17. **Expansion only:** Patients treated with prior endocrine therapy

18. Known impaired cardiac function or clinically significant cardiac disease such as uncontrolled supraventricular arrhythmia, ventricular arrhythmia requiring therapy, or congestive heart failure (New York Heart Association functional class III or IV)

19. Myocardial infarction or unstable angina within 6 months prior to first dose of study drug

20. Known myelodysplastic syndrome

21. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy, or any other condition that could compromise safety or the patient's participation in the study

22. Impairment of gastrointestinal function (i.e., diagnosis of malabsorption syndrome) that may significantly alter the absorption of ZEN003694 or talazoparib

23. Other known active cancer requiring therapy at time of study entry or that progressed or required treatment within 3 years prior to starting study drug (except for skin basal cell carcinoma or squamous cell carcinoma or in situ cervical cancer)

24. Historically positive (screening tests not required) for human immunodeficiency virus (HIV); or hepatitis B virus (HBV) with currently active disease defined as hepatitis B surface antigen (HBsAg) positivity; or hepatitis C virus (HCV) unless previously treated and viral load is undetectable.

25. Major surgery other than diagnostic surgery, dental surgery or stenting within 4 weeks prior to the first administration of study drug

26. Concurrent participation in another clinical investigational treatment trial with a systemic therapy

27. Any other reason that in the opinion of the Investigator would prevent the patient from completing participation or following the study schedule

7. STUDY DRUG AND MATERIALS

7.1 ZEN003694 Administration

For this study ZEN003694 is to be ingested with a full (8-ounce) glass of water at least 1 hour before eating or 2 hours after eating (fasting). Each capsule should be swallowed whole. Patients should be advised not to chew, dissolve, or open the capsules.

In Part 1 (dose escalation), the RP2D of ZEN003694 was established as 48 mg once daily.

In Part 2 and Expansion, ZEN003694 will be administered as 48 mg once daily.

7.1.1 Precautions

Patients should also be advised to minimize their exposure to sunlight.

[redacted]

Patients should be provided 'filled' prescriptions for an anti-emetic, if possible, or ensure patients fill their prescriptions of an anti-emetic on the first day of dosing (C1D1). Patients are to be instructed to take the anti-emetic at first signs of nausea.

7.1.2 ZEN003694 Formulation

ZEN003694 capsules for oral administration are supplied as 12 mg and 48 mg capsules containing ZEN003694 as the active substance with no additional excipients filled in the capsule. The 12 mg ZEN003694 capsules are size 3, Swedish orange, hard gelatin capsules and the 48 mg ZEN003694 capsules are size 0, white opaque, hard gelatin capsules.

The drug substance is manufactured under Good Manufacturing Practice conditions [redacted] The drug product is manufactured, packaged and labeled [redacted] Capsules are packaged in high density polyethylene opaque, white resin bottles with screw-cap, child-resistant closures.

7.1.3 Storage Conditions

ZEN003694 should be securely stored at room temperature 20° – 25°C (68° – 77°F) (excursions from 15° – 30°C [59° – 86°F] are permitted). Protect from light and do not freeze.

7.2 Talazoparib Administration

Talazoparib will be administered as a 1 mg once daily dose (as a starting dose in dose escalation, Part 1) and will be taken at the same time as ZEN003694, at approximately the same time each day. In Part 2 and Expansion, talazoparib will be administered at a starting dose of 0.75mg once daily. As with ZEN003694, talazoparib is to be self-administered at least 1 hour before eating or

2 hours after eating (fasting). Talazoparib capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them. Subjects should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

7.2.1 Talazoparib Formulation

Talazoparib (also known as MDV3800, BMN 673) has the chemical name (8S,9R) 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-pyrido[4,3,2-de]phthalazin-3-one (provided as the 4 methylbenzenesulfonate [tosylate] salt). The drug substance is formulated with silicified microcrystalline cellulose. The product will be provided as powder filled, hard gelatin capsules containing talazoparib in strengths of 1.0 mg and 0.25 mg. The capsules for each dose strength will be provided in dose specific colors. Additional details will be provided in a pharmacy binder.

7.2.2 Talazoparib Handling and Storage Conditions

Talazoparib should be securely stored at room temperature. Protect from light and do not freeze. Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment (**Goodin, et al., 2011**). Subjects should be advised that oral anticancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

7.3 Study Drug Dispensation

Study drugs are to be dispensed in the study clinic on a cycle-by-cycle basis, at Day 1 of each 28 day cycle. Additional drug supplies may be dispensed mid-cycle to cover the needs due to any dose modifications. Quantities dispensed on Day 1 of each cycle should cover the needs for 28 days of daily dosing, plus supplies for an extra 1-3 days of dosing should a patient need to delay their visit to start the next cycle.

NOTE: During the COVID-19 pandemic, drug supplies may be dispensed (shipped by courier) by the study clinic's pharmacy directly to the study patient's home. Upon deliver, a signature of receipt by the patient is required. A copy of the signed receipt is to retained and returned to the study clinic (by either scan/email or held and returned at the time the patient returns for their next visit). In addition, at the time of receipt, the patient is to complete a form acknowledging the number of bottles received and the condition in which they were received. The acknowledgement form should also be scanned/emailed to the clinic or returned by the patient at their next visit. The pharmacy/clinic staff are to follow-up by phone call within 2 days of the drug shipment to ensure the patient received drug supplies.

7.4 Study Drug Accountability

The Investigator, pharmacist or qualified designee is responsible for making an inventory of study drug (both ZEN003694 and talazoparib) upon receipt. All used and unused study drug must be retained until final reconciliation or as indicated by the Sponsor. The study drug is to be administered/dispensed by the Investigator or appropriately qualified site personnel named on the delegation of authority log. Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Although appropriate personnel may be designated

to administer/dispense drug and maintain drug accountability records, the Investigator is ultimately responsible for all drug accountability.

The Investigator or designee must maintain accurate records of the receipt, disposition and return of study drug (ZEN003694 and talazoparib). Documentation of drug disposition/return should identify the patient receiving the study drug, the quantities (by dosage strength) of study drug dispensed/returned and dates study drug were dispensed/returned/destroyed. This documentation is required in addition to drug accountability information recorded on case report forms (CRFs). A copy of the reconciled drug inventory record will be provided to the Sponsor or its designee, and the study site will retain the original record. A written explanation must be provided for any discrepancies.

The Sponsor's representatives will authorize the return or destruction of all used, partially used, and unused bottles of study drug. If the study site is capable of destroying study drug it may do so upon authorization by the Sponsor. Records will include date of destruction or return, and quantities destroyed or returned to the Sponsor or its designee. Detailed instructions on study drug accountability will be provided in a study reference manual.

7.5 Treatment Compliance

Trained study personnel will dispense ZEN003694 and talazoparib and will instruct patients to take their study medication at least 1 hour before eating or 2 hours after eating (fasting). Treatment compliance will be monitored by the review of the patient's dosing diary and drug accountability records. Study treatment administration data will be recorded in the patient's medical record and on the Drug Administration CRFs.

8. STUDY TREATMENT GUIDELINES

8.1 Guidelines for Management of Treatment-Related Toxicity

In Part 1 (dose escalation), dose holds of ZEN003694 and talazoparib are allowed in Cycle 1. If a dose hold is indicated for the management of a treatment related toxicity to ZEN003694 and/or talazoparib, both ZEN003694 and talazoparib doses are to be held. In Cycle 1 of the dose escalation phase, dose reduction of ZEN003694 is not allowed; however the dose of talazoparib may be reduced from the initial 1.0 mg dose in 0.25 mg increments in accordance with the talazoparib label and by agreement with Zenith. For guidance regarding drug-related toxicities that qualify as a DLT in Cycle 1 of the dose escalation phase of the study, refer to Section **5.1.2**.

In Part 1, beyond Cycle 1 and at any time in Part 2 (Simon 2-stage) or in the Expansion phase, dose holds or dose reductions are allowed for both ZEN003694 and talazoparib. Intra-patient dose reductions of talazoparib are allowed in 0.25mg increments. Intra-patient dose reductions of ZEN003694 are allowed in 12mg to 24mg increments. All dose reductions should be based on prior approval by the Sponsor. Dose holds and reductions are to be managed by the guidelines set forth in Sections **8.2** and **8.3**.

8.2 Management of Selected Talazoparib-Related Toxicities

For toxicities of anemia, neutropenia and abnormal liver tests (regardless of severity), the dose of talazoparib should be held and/or reduced prior to holding or making any changes in the dosing of ZEN003694. If these toxicities are not managed by a talazoparib dose hold or reduction, the dosing of ZEN003694 can be held and/or modified with Zenith's approval.

For Grade 3/4 anemia, neutropenia, abnormal liver tests, thrombocytopenia and clinically significant laboratory events, the dosing of talazoparib and ZEN003694 should follow the guidelines outlined in **Table 6**. Prior to making any changes in dosing, the Investigator is to obtain agreement by the Sponsor. For Grade 1/2 anemia, neutropenia and abnormal liver tests, no dose reductions are required however, should the Investigator elect to hold dosing, the dose of talazoparib should be held first prior to holding ZEN003694 dosing.

For the management of all other treatment related toxicities (except Grade3/4 anemia, neutropenia and abnormal liver tests), the guidelines outlined in **Table 7** should be followed. If a dose hold is indicated, the doses of both talazoparib and ZEN003694 are to be held. If a dose modification is indicated, doses of talazoparib and/or ZEN003694 may be modified (except in Cycle 1 of dose escalation) based upon the Sponsor's approval.

Table 6: Management of Selected Grade 3/4 Talazoparib-related Toxicities

Selected Toxicity	Talazoparib and ZEN003694 management
Grade 3 or 4 Anemia (hemoglobin < 8.0 g/dL)	Hold talazoparib only and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9 g/dL or better, then resume talazoparib at a reduced dose.

	• If anemia with hemaglobin < 8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. ZEN003694 may also be held with agreement by the Sponsor. Monitor weekly until hemoglobin returns to 9.0 g/dL (Day 1), then resume talazoparib at a further reduced dose. The dose of ZEN003694 may also be modified with agreement by the Sponsor. • If anemia persists for >4 weeks without recovery of hemoglobin to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and ZEN003694 and consider referral to a hematologist. Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.
Grade 3 or 4 Neutropenia (ANC < 1000/µL)	Hold talazoparib only and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/µL, then resume talazoparib at a reduced dose. • If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. ZEN003694 may also be held with agreement by the Sponsor. Monitor weekly until ANC ≥1500/µL, then resume talazoparib at a further reduced dose. The dose of ZEN003694 may also be modified with agreement by the Sponsor. • If neutropenia persists for >4 weeks without recovery to ≥1500/µL at any dose level despite supportive care measures, discontinue talazoparib and ZEN003694 and consider a referral to a hematologist. G-CSF and GM-CSF may be used at investigators discretion for the supportive treatment of neutropenia at any occurrence.
Grade 3 or 4 Thrombocytopenia (platelets < 50,000/µL)	Hold talazoparib and ZEN003694 and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/µL, then resume talazoparib at a reduced dose. Resume ZEN003694 at the same or reduced dose with agreement by the Sponsor. **Note:** If platelet

	counts are increasing but have not fully recovered to at least 75,000/μL, dosing may be restarted based on discussion and approval by the Sponsor. • If thrombocytopenia (<50,000/μL) recurs after one dose reduction, hold talazoparib and ZEN003694 and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/μL, then resume talazoparib and ZEN003694 at the same dose or, with agreement by Zenith, at a reduced dose. • If thrombocytopenia persists for >4 weeks without recovery to ≥ 50,000/μL despite supportive care measures, discontinue talazoparib and ZEN003694 and consider a referral to a hematologist. Thrombopoietin analogues and/or platelet transfusions may be used at investigators discretion for the supportive treatment of thrombocytopenia at any occurrence.
Grade 3 or 4 Laboratory events determined to be clinically significant, except for: a) Grade 3/4 Liver, Anemia, Neutropenia, or Thrombocytopenia (as listed in this table); and b) Grade 3/4 amylase or lipase elevations that are not associated with manifestations of pancreatitis	Hold talazoparib and ZEN003694 for any Grade ≥ 3 laboratory events. If after a 14 day hold the toxicity has resolved to a Grade ≤ 1 (or to a baseline grade level) resume talazoparib at a reduced level per the talazoparib dosing label and at a reduced level of ZEN003694 with agreement by the Sponsor. If laboratory abnormality does not resolve to Grade ≤ 1 after 14 days, both talazoparib and ZEN003694 are to be permanently discontinued All Grade 3/4 amylase or lipase elevations should be discussed with the Sponsor's Medical Monitor.
Grade 3 or 4 Abnormal Liver tests	Hold talazoparib alone if any of the following occur: • Subjects who develop AST or ALT > 5 x ULN (without TBili >2 x ULN) **OR** • Subjects with baseline total bilirubin ≤1.5 x ULN who subsequently present with > 3 x ULN **OR** • Subjects with baseline total bilirubin > 1.5 x ULN and ≤ 3 x ULN (e.g., Gilberts) who subsequently present with bilirubin > 5 x ULN

	If abnormalities resolve to baseline values within 2 weeks, there are no signs of drug-induced liver injury, and none of the permanent discontinuation criteria are met (listed below), then upon discussion with the Sponsor, the investigator may resume talazoparib at a reduced dose level. **Criteria for Permanent Discontinuation of Both Study Drugs in Association with Liver Test Abnormalities if any of the following occur:** • Subjects who develop with AST **OR** ALT values >3 × ULN **AND** a Tbili value >2 × ULN • Subjects with AST/ALT >5 × ULN that persists for more than 7 days (AST/ALT >8 × ULN for subjects with hepatic involvement). • Subjects with AST/ALT >20 × ULN that persists for longer than 3 days • Subjects with Tbili >3 × ULN that persists for longer than 7 days (>5 × ULN for subjects with Gilbert's disease).

8.3 Management Guidelines for All Other Toxicities (not listed in Section 8.2, Table 6)

For all other treatment related toxicities not listed in **Table 6**, dose holds and reductions of both talazoparib and ZEN003694 should be managed according the guidelines in **Table 7**. If a toxicity requires a dose hold, the doses of both talazoparib and ZEN003694 are to be held. If a dose change is required, the next lower dose of both or either talazoparib and ZEN003694 should be discussed and approved by the Sponsor.

Table 7: Guidelines for Dose Holds and Dose Reductions of both Talazoparib and ZEN003694

Event	Other Toxicities (not listed in Section 8.2, Table 6)*
Grade 1	No change
Grade 2	No change required; but a dose hold of both ZEN003694 and talazoparib for Grade 2 laboratory toxicity or a laboratory trend of concern is allowed based on Investigator discretion. For dose holds due to Grade 2 anemia, neutropenia or abnormal liver tests: hold talazoparib dosing first prior to holding ZEN003694 dosing. In cases where doses are held, if toxicity or trend is reduced to a Grade 1 within 14 days*, treatments will resume at the original dose level for the first event, and at the next lower dose level for a subsequent event, with mutual agreement between the Investigator and the Sponsor.
Grade 3	Hold both ZEN003694 and talazoparib treatments. If toxicity (except for those noted in **Table 6**) resolves to baseline or Grade 1 within 14 days*, resume treatments and reduce the dose of both ZEN003694 and talazoparib by one dose level (except in Cycle 1 of dose escalation). If toxicity has not resolved to at least a Grade 1 toxicity within 14 days of a dose hold, permanently discontinue talazoparib and ZEN003694.
Grade 4	Hold both ZEN003694 and talazoparib treatments. Except for toxicities noted in **Table 6**; if toxicity is resolved to Grade ≤ 1 within 14 days*, resume treatments at one dose level below (except in Cycle 1 of dose escalation) with mutual agreement between the Investigator and Sponsor. If toxicity has not resolved to a Grade ≤ 1 within 14 days of a dose hold permanently discontinue talazoparib and ZEN003694.

* Dose interruption caused by any toxicities lasting longer than 14 days (hematologic or non-hematologic toxicity) will result in study drug discontinuation of both ZEN003694 and talazoparib.

8.4 Intra-Patient Dose Escalation in Part 2, Simon 2-Stage

For patients enrolled in Part 2 of the study (Simon 2-Stage), intra-patient dose escalations are allowed based upon agreement between the Investigator and the Sponsor. Dose escalation up to a maximum of 48mg ZEN003694 and/or 1.0mg Talazoparib will be allowed only after tolerability and laboratory results have been shown to be stable for 2 cycles.

8.5 Concomitant Medications and Therapies

8.5.1 Prohibited Concomitant Medications and Therapies

ZEN003694 is primarily metabolized by CYP3A4. Therefore, strong inhibitors and inducers of CYP3A4 must be excluded during ZEN003694 administration. [redacted] substrates of CYP1A2 with narrow therapeutic ranges must be avoided. If use of a strong CYP3A4 inhibitor or inducer, or CYP1A2 substrate with a narrow therapeutic range cannot be avoided, then the patient must discontinue the study.

Use of moderate CYP3A4 inhibitors and inducers or significant CYP1A2 substrates will be determined on a case-by-case basis at the discretion of the Investigator and with approval from the Sponsor.

A list of CYP3A4 inhibitors and inducers and CYP1A2 substrates that should be avoided are listed in **Table 8**. This list is not comprehensive; when considering use of a medication that could be a potential CYP3A4 inhibitor or inducer or CYP1A2 substrate, the Investigator should consult with the Sponsor.

In addition, **Table 8** contains a list of strong P-gp inhibitors that should be avoided during concomitant treatment with talazoparib. Strong P-gp inhibitors are defined as the P-gp inhibitors that result in ≥ 2-fold increase in the exposure of an in vivo probe P-gp substrate according to the University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org)

Table 8: Inhibitors and Inducers of Relevant Drug-metabolizing Enzymes

Category	Inhibitors of CYP3A4 (May increase ZEN003694 exposure)	Inducers of CYP3A4 (May decrease ZEN003694 exposure)	Substrates of CYP1A2* [redacted]	Inhibitors of P-gp
AVOID	boceprevir clarithromycin conivaptan grapefruit juice indinavir itraconazole ketoconazole lopinavir/ ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	avasimibe rifampin St. John's wort	ramelteon tizanidine theophylline	amiodarone carvedilol clarithromycin cobicistat dronedarone erythromycin glecaprevir/ pibrentasvir indinavir itraconazole ketoconazole lapatinib lopinavir propafenone quinidine ranolazine ritonavir saquinavir sofosbuvir/ velpatasvir/voxi- laprevir telaprevir tipranavir valspodar verapamil

Source: http://www fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

*NOTE: Exposure to the following substrates of CYP1A2 [redacted] associated toxicity should be closely monitored: alosetron, duloxetine, melatonin, tacrine

Caution should be used for coadministration of other P-gp inhibitors: (e.g., atorvastatin, azithromycin, conivaptan, diltiazem, diosmin, eliglustat, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract) and BCRP inhibitors (curcumin, cyclosporine, elacridar [GF120918]).

Any CYP3A4 inhibitors or inducers; CYP1A2 substrates; P-gp inhibitors or inducers; or BCRP inhibitors taken by the patient during the study period must be documented in the patient's chart and on the Concomitant Medications CRF. If the Sponsor's approval is not obtained prior to administration of these medications, the patient may be withdrawn from the study by the Sponsor.

Because of the known risk of QT/QTc prolongation from 5-hydroxytryptamine type 3 (5-HT3)

receptor anti-emetics, 5-HT3 receptor antagonist antiemetic drugs should be used with Investigator discretion, if alternative drugs are not available. Dolasetron should be avoided, as the prolongation of QTc may be greater with this drug based upon American Society of Clinical Oncology (ASCO) guidelines (**Basch, et al., 2011**). To date, ZEN003694 has shown no evidence of QT prolongation, suggesting that drugs such as 5-HT3 antagonists may be safely used concomitantly where indicated by the Investigator's clinical judgment.

Concomitant endocrine-based therapies for breast cancer are prohibited in this study.

Therapeutic anticoagulation with warfarin, apixaban, or other anti-factor agents (Factor Xa inhibitors and Factor IIa inhibitors) are not permitted (i.e., rivaroxaban, apixaban, betrixaban, edoxaban otamixaban, letaxaban, eribaxaban, dabigaran). Low-dose warfarin for maintenance of port patency or prophylactic anti-platelet agents are allowed.

During the study, other chemotherapy, immunotherapy, radiation (except, if ≤ 5 fractions for palliative care of solitary lesions), bone-targeting radionuclides, or surgery are also prohibited.

8.5.2 Permitted Concomitant Medications and Therapies

Use of corticosteroids is allowed up to a daily dose of 10 mg prednisone or equivalent provided that the dose has been stable for at least 2 weeks prior to the start of ZEN003694 dosing and will remain stable during ZEN003694 treatment.

Treatment with anti-emetic therapy will be permitted, if clinically indicated. Based on experience in previous ZEN003694 trials, Investigators are instructed to prescribe prophylactic use of anti-emetics for any possible GI intolerance and instruct patients to maintain adequate hydration during the course of treatment. Patients should be provided ‘filled’ prescriptions for an anti-emetic, if possible, or ensure patients fill their prescriptions of an anti-emetic on the first day of dosing (C1D1).

Treatment with filgrastim or other colony stimulating factors will be permitted for Grade 3 or higher hematologic toxicity as per Package Insert, but may not be used prophylactically. Patients should receive full supportive care, including hematopoietic growth factors based upon ASCO guidelines (**Smith, et al., 2015**), if clinically indicated.

Treatment required for care of complications/adverse events arising from the cancer and/or treatment will be permitted. All concomitant medications must be recorded on the Concomitant Medications CRF.

9. STUDY VISIT PROCEDURES AND ASSESSMENTS

The Schedule of Assessments (**Table 1**) provides an overview of the timeline when clinic visits and assessments are to be performed during the course of the study. This section provides a detailed description of required evaluations and assessments during each scheduled study visit.

9.1 Study Procedures by Visit

All scheduled study visits are to occur within ± 3 days of the specified dates outlined in **Table 1**. All visits are to be scheduled relative to Cycle 1 Day 1 regardless if a intervening scheduled visit is missed or rescheduled, or if doses were held or missed. All assessments and sample collections required during a specific study visit are to be performed prior to study drug administration to be given in the clinic, unless otherwise specified.

NOTE: During the COVID-19 pandemic, the following prospective deviations are allowed for the non-assessment of the following, only if a patient is unable to attend an in-clinic visit: physical examinations, vital signs, weight, ECOG, PK blood draws, PD blood draws, and biopsies. In-clinic visits are mandatory at Cycle 1, Days 1 and 15; and on Day 1 of all Cycles.

9.1.1 Screening Visit

All screening tests must be performed within 28 days before the first day of treatment (Cycle 1, Day 1). The informed consent form (ICF) must be signed before screening procedures are performed (see Section **9.2.1**).

Screening will include:

- Collection of information on status of inclusion and exclusion criteria (see Section **9.2.2**)
- Complete medical history, including cancer history, prior cancer-related surgery and treatments, and demographic history (see Section **9.2.3**)
- Listing of all medications taken within 21 days of enrollment and any ongoing medications
- Physical examination including height (cm) and weight (kg) (see Sections **9.2.4** and **9.2.5**)
- ECOG performance status (see Section **9.2.6** and **Appendix 1**)
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate) (see Section **9.2.7**)
- Hematology (see Section **9.2.8**)
- Coagulation tests (see Section **9.2.8**)
- Serum chemistries (see Section **9.2.8**)
- Calculated creatinine clearance (see Section **9.2.8**)
- Serum or urine pregnancy test (see Section **9.2.8**)

- Urinalysis with quantitative biochemical analyses of urinary protein, albumin and creatinine and calculated protein:creatinine ratio and albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory. (see Section **9.2.8**)

- HIV/HBV/HCV test (China only)

- 12-lead ECG: triplicate ECGs if QTc > 500msec (see Section **9.2.9**)

- [redacted]

- Quality of Life: QLQ-C30 and QLQ-BR23 completion by patient

- Fresh tumor biopsy samples (US and EU only), archival tumor slides (US and EU only) (see Section **9.2.11**). The screening biopsy may be performed up to 6 weeks prior to the first dose of study drug.
- Tumor assessment (see Section **9.2.15**) Imaging for tumor assessments must be performed within 4 weeks of the first dose of study drug (C1D1)

- **Parts 1 and 2** Germline BRCA1/2 mutation assessment: For patients who have prior documentation of gBRCA mutation status, a blood sample for gBRCA testing is not required to be collected nor shipped to Myriad Genetics. If prior testing of gBRCA status has not been performed, either a blood sample can be collected and shipped to Myriad Genetics or if your Institution has a qualified NGS testing panel a blood sample may be tested using your platform. Reports showing the panel of genes tested to establish BRCA1/2 mutation status are to be provided to the Sponsor.
- **In EXPANSION Cohort A only:** Germline BRCA1/2 mutation status: If no prior documentation of BRCA1/2 mutation status is known, a sample will be collected and sent by ambient shipping to Myriad genetics for BRACAnalysis CDx. If prior documentation of BRCA1/2 mutation status by BRACAnalysis CDx performed by Myriad Genetics is not available, a screening blood sample will be collected and frozen and stored for retrospective analysis at Myriad Genetics. For patients who have prior documentation of BRCA mutation status by BRACAnalysis CDx, a blood sample for possible retrospective BRCA germline testing should NOT be collected.
- **In EXPANSION Cohort B and C:** Germline BRCA1/2 mutation assessment: For patients who have prior documentation of gBRCA mutation status, a blood sample for gBRCA testing is not required to be collected. If prior testing of gBRCA status has not been performed, either a blood sample can be collected and shipped to Myriad Genetics or another equivalent test may be performed. Reports showing the panel of genes tested to establish BRCA1/2 mutation status are to be provided to the Sponsor.
-

9.1.2 Cycle 1

Day 1 (Pre-dose)

- Symptom-directed physical examination and weight

- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Coagulation tests
- Serum chemistries
- Urine pregnancy test (see Section **9.2.8**)
- Urinalysis with quantitative biochemical analyses of urinary protein, albumin and creatinine and calculated protein:creatinine ratio and albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory. (see Section **9.2.8**)
- 12-lead ECG: triplicate ECGs if QTc > 500msec
- PK sample for ZEN003694/ZEN003791 (see Section **9.2.10**) (in Part 1 only)
- PD samples for whole blood BET inhibitor and PARP inhibitor PD marker expression (in Part 1 only) (see Section **9.2.11**)
- PD samples: in whole blood for ctDNA (US and EU sites only): samples will be banked for possible future analysis (see Section **9.2.11**)
- AEs
- [redacted]
- Quality of Life: QLQ-C30 and QLQ-BR23 completion by patient
- Concomitant medications

Day 1 (Dosing)

- ZEN003694 and talazoparib at least 1 hour before eating or 2 hours after eating

Day 1 (Post-dose)

- PK samples for ZEN003694/ZEN003791: (in Part 1 only)
  - 15 minutes (±5 min), 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±10 min), 4 hours (±15 min), 6 hours (±15 min) and 8 hours (±30 min) post-ZEN003694 and talazoparib doses
- PD samples: whole blood for BET inhibitor and PARP inhibitor PD marker expression (Part 1 only) at 2 hours (±15 min), 4 hours (±15 min), and 6 hours (±15 min) and 8 hours (±15 min) post- ZEN003694 and talazoparib doses (Part 1 only)

- AEs
- Concomitant medications

Days 2 – 28 (Dosing)

- ZEN003694 and talazoparib daily at least 1 hour before eating or 2 hours after eating

  Note: Instruct patients not to take study drug and talazoparib before their clinic visits on Days 8, 15 and 22.

Day 8 (Pre-dose): During the COVID-19 pandemic, this visit may be performed as a telephone visit

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Serum chemistries
- Fresh tumor biopsy: **In Parts 1 and 2**, to be collected on C1D8, C1D9 or C1D10 if the biopsy is from a palpable lesion (or from other lesions, at the Investigator's discretion). In the **Expansion phase**, biopsies are to be collected between C1D8 and C1D14, or within ±14 days of the C3D1 visit (if biopsy was not collected in Cycle 1). If tumor is accessible, biopsies are mandatory in the US and EU. The biopsy should be collected 2-4 hours after ZEN003694 dosing, if possible (see Section **9.2.11**); and should be collected from the same tissue location as the screening biopsy, if possible. The dosing date and time of the dose taken just prior to the biopsy is to be recorded.
- AEs
- Concomitant medications

Day 15 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Coagulation tests
- Serum chemistries

- PK sample for ZEN003694/ZEN003791 (Part 1 only)
- PK sample for talazoparib (Part 1 only): (Pre-dose sample collection should be at least 20 hours after the previous dose of talazoparib. Instruct patients to not take their study drugs in the morning before their clinic visit.)
    - The PK collection date, exact collection time, study drug doses taken and dosing time for both study drugs are to be recorded in source documents and in the eCRF.
    - On the day prior to the C1D15 PK collections, the date, dosing time and study drug doses taken and dosing time for both study drugs are to be recorded in source documents and in the eCRF.
    - In the event the C1D15 pre-dose PK samples cannot be collected (or is not collected), 'makeup samples' should be collected on a later date using the same criteria
- AEs
- Concomitant medications

Day 22 (Pre-dose): If intermittent dosing is implemented and/or if there is a need to change the cycle duration from 28 days to 21 days, the Day 22 assessments will not be required. **During the COVID-19 pandemic, this visit may be performed as a telephone visit**

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Serum chemistries
- AEs
- Concomitant medications

9.1.3 Cycle 2

Day 1 (Pre-dose)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology

- Coagulation tests
- Serum chemistries
- Urine pregnancy test: serum pregnancy test will be required if the urine pregnancy test is positive (see Section **9.2.8**)
- Urinalysis with quantitative biochemical analyses of urinary protein, albumin and creatinine and calculated protein:creatinine ratio and albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory. (see Section **9.2.8**)
- 12-lead ECG: triplicate ECGs if QTc > 500msec
- PK sample for ZEN003694/ZEN003791
- PK sample for talazoparib (Parts 1 and 2, and Expansion Cohorts A and C): (Pre-dose sample collection should be at least 20 hours after the previous dose of talazoparib. Instruct patients to not take their study drugs in the morning before their clinic visit.)
    - The PK collection date, exact collection time, study drug doses taken and dosing time for both study drugs are to be recorded in source documents and in the eCRF.
    - On the day prior to the C2D1 PK collections, the date, dosing time and study drug doses taken and dosing time for both study drugs are to be recorded in source documents and in the eCRF.
    - In the event the C2D1 pre-dose PK samples cannot be collected (or is not collected), 'makeup samples' should be collected on a later date using the same criteria
- AEs
- [redacted]
- Quality of Life: QLQ-C30 and QLQ-BR23 completion by patient
- Concomitant medications

Day 1 (Post-dose)

- PK samples for ZEN003694/ZEN003791:
    - 1 hour (±5 min), 2 hours (±10 min) and 4 hours (±15 min) post-ZEN003694 and talazoparib doses

Days 1 – 28 (Dosing)

- ZEN003694 dosing and talazoparib daily at least 1 hour before eating or 2 hours after eating

  Note: Instruct patients to not take study drug and talazoparib before their clinic visit on Day 15.

Day 8 (The Cycle 2, Day 8 visit will only include blood draws for safety laboratory testing and may be drawn in the morning after the patient has taken his/her dose. Testing may be drawn at a laboratory local to the patient's home)

- Hematology
- Serum chemistries

Day 15 (Pre-dose): During the COVID-19 pandemic, this visit may be performed as a telephone visit

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Serum chemistries
- PK sample for ZEN003694/ZEN003791
- PK sample for talazoparib (Parts 1 and 2, and Expansion Cohorts A and C): (Pre-dose sample collection should be at least 20 hours after the previous dose of talazoparib. Instruct patients to not take their study drugs in the morning before their clinic visit.)
    - The PK collection date, exact collection time, study drug doses taken and dosing time for both study drugs are to be recorded in source documents and in the eCRF.
    - On the day prior to the C2D15 PK collections, the date, dosing time and study drug doses taken and dosing time for both study drugs are to be recorded in source documents and in the eCRF.
    - In the event the C2D15 pre-dose PK samples cannot be collected (or is not collected), 'makeup samples' should be collected on a later date using the same criteria.
- Tumor assessments (RECIST): Expansion only: at Cycle 2 Day 15 (± 7 days)
- AEs
- Concomitant medications

Day 22 (The Cycle 2, Day 22 visit will only include blood draws for safety laboratory testing and may be drawn in the morning after the patient has taken his/her dose. Testing may be drawn at a laboratory local to the patient's home). If intermittent dosing is implemented and/or if there is a need to change the cycle duration from 28 days to 21 days, the Day 22 assessments will not be required.

- Hematology
- Serum chemistries

9.1.4 Cycles 3 and onward

Day 1 (Pre-dose, ± 3 days unless otherwise stated)

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Coagulation tests
- Serum chemistries
- Urine pregnancy test: serum pregnancy test will be required if the urine pregnancy test is positive (see Section **9.2.8**)
- Urinalysis with quantitative biochemical analyses of urinary protein, albumin and creatinine and calculated protein:creatinine ratio and albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory. (see Section **9.2.8**)
- 12-lead ECG: (at Cycle 3 and every 2 cycles) triplicate ECGs if QTc > 500msec
- Tumor assessments (RECIST v1.1): Parts 1 and 2 only: (at Cycle 3 Day 1 and every 2 cycles; ± 7 days)
- Tumor assessments (RECIST v1.1): Expansion only: Every 6 weeks (± 7 days): **at Day 15** in Cycles 2, 5, 8, 11, 14, 17, 20, etc.; **and at Day 1** in Cycles 4, 7, 10, 13, 16, 19, etc.
- PD samples: whole blood for ctDNA (at Cycle 3 only for possible future analysis) (US and EU sites only)
- Fresh tumor biopsy samples from US and EU patients only(at Cycle 3 only; ± 14 days; if not collected at Cycle 1, Days 8-14) should be collected 2-4 hours after ZEN003694 dosing, if possible (see Section **9.2.11**), and should be collected from the same tissue location as the screening biopsy, if possible.
- AEs

- Quality of Life: QLQ-C30 and QLQ-BR23 completion by patient
- Concomitant medications

Days 1 – 28 (Dosing)

- ZEN003694 and talazoparib at least 1 hour before eating or 2 hours after eating

  Note: Instruct patients not to take ZEN003694 and talazoparib before their clinic visit on Day 1 of each cycle.

Day 15 (For Cycles 3 and onwards, the Day 15 visit blood draws for safety laboratory testing may be drawn in the morning after the patient has taken their dose. Testing may be drawn at a laboratory local to the patient's home). In Cycle 6 and onward, the Day 15 hematology and serum chemistry tests may be waived at the discretion of the Investigator if platelet counts are stable and there are no other laboratory concerns.

- Hematology
- Serum chemistries

9.1.5 Unscheduled Visit

The following assessments and tests are to be performed during an unscheduled visit along with any others as clinically indicated: Other protocol specific tests may be requested and performed per Sponsor requirement:

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Serum chemistries
- Coagulation
- Urinalysis
- Quantitative urinary analysis
- AEs
- Concomitant medications

9.1.6 End of Treatment Visit

The following assessments are to be performed within one week (± 3 days) of discontinuation of ZEN003694 treatment: If a subject's dose was held and treatment was not resumed after a two

week period, the scheduling of the EOT visit from the date of last study drug is extended to 14 days ±3 days.

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology
- Serum chemistries
- Urine pregnancy test: serum pregnancy test will be required if the urine pregnancy test is positive (see Section **9.2.8**)
- Urinalysis with quantitative biochemical analyses of urinary protein, albumin and creatinine and calculated protein:creatinine ratio and albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory. (see Section **9.2.8**)
- Tumor assessments (RECIST v1.1): (Only if the EOT visit is > 6 weeks from the time of the prior tumor assessment)
- PD sample: whole blood for ctCNA (for possible future analysis) (US and EU only)
- [redacted]
- Quality of Life: QLQ-C30 and QLQ-BR23 completion by patient
- Fresh tumor biopsy sample (only if possible, at the time of progression) (US and EU only)
- AEs
- Concomitant medications

9.1.7 Safety Follow-up Visit

The Safety Follow-up visit is to occur 30 days (±3 days) after the End of Treatment visit, or prior to beginning a new anti-cancer treatment, whichever occurs first. If a new cancer therapy is started within 7 days following the End of Treatment visit, the Safety Follow-up visit is not required.

The Safety Follow-up visit is to include the following assessments:

- Symptom-directed physical examination and weight
- ECOG performance status
- Vital signs (temperature [ºF/ºC], blood pressure and heart rate)
- Hematology

- Serum chemistries
- Urinalysis with quantitative biochemical analyses of urinary protein, albumin and creatinine and calculated protein:creatinine ratio and albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory. (see Section **9.2.8**)
- AEs
- Concomitant medications

9.1.8 Cross-Over of Expansion Cohort B ZEN003694 Monotherapy Patients

Patients enrolled in Expansion Cohort B on single agent ZEN003694 who have confirmed radiographic progression by RECIST v1.1 criteria will have the choice to cross-over to treatment with ZEN003694 in combination with talazoparib. Patients may cross-over to the combination treatment at the time of disease progression but no sooner than after 6 weeks of receiving ZEN003694 monotherapy. Participation in the cross-over phase is optional for these patients.

To participate in the cross-over phase, patients are required to complete an End of Treatment visit for Cohort B monotherapy and sign the cross-over informed consent form. Once signed, patients will be evaluated for eligibility to receive ZEN003694 in combination with talazoparib. The inclusion/exclusion criteria and screening assessments for the cross-over combination treatment will be same as those criteria and assessments for patients enrolled in Expansion Cohort B (monotherapy).

The ZEN003694 monotherapy End of Treatment (EOT) visit, the signing of the cross-over consent, and the subsequent evaluation of the screening assessments may all be performed on the same day. The EOT visit assessments may be used as the screening assessments for the cross-over study. All screening assessments must be performed and eligibility criteria met within 14 days from the date of the EOT visit and the start of cross-over combination treatment at C1D1. Cross-over patients will be evaluated for safety and efficacy by protocol assessments as required for all patients enrolled in the Expansion cohorts as detailed in **Table 1**.

Blinded independent central review of tumor assessments is not required in the cross-over phase of the study. Upon discontinuation from the cross-over phase of the study, subjects are required to complete End of Treatment and Safety Follow-up visits as set forth in **Table 1.**

9.2 Study Assessments

9.2.1 Informed Consent

The Investigator or designee must present and explain the study protocol to prospective study patients before any study-specific screening procedures are performed. The ICF presented to the patient must be in a language that the patient can read and understand. Once the patient has had an opportunity to read the ICF, the Investigator or designee must be available to answer any questions the patient may have regarding the study protocol and procedures. The Investigator or designee must explain that the patient is not obliged to enter the study, and is free to withdraw

from it at any time for any reason. If new safety information becomes available and results in significant changes in risk/benefit assessment, the ICF should be reviewed and updated if necessary. Under this circumstance, all patients, including those already being treated, should be given the new information, given a copy of the revised ICF, and allowed to re-evaluate their consent to continue in the study.

A copy of the signed and dated ICF will be provided to the patient. The Investigator will retain the original signed ICF.

9.2.2 Inclusion/Exclusion Criteria

Review the inclusion/exclusion criteria (Section **6**) at the Screening visit to ensure that the patient qualifies for the study. The patient may be enrolled into the study if inclusion criteria are met and none of the exclusion criteria are met.

9.2.3 Medical History and Demographics

Obtain a complete medical history (significant past and ongoing conditions) including cancer history, prior cancer treatments and surgeries, and demographic information at the Screening visit. Previous history of allergies/ allergic reactions should also be captured on the Medical History eCRF.

9.2.4 Physical Examination/Symptom-directed Physical Examination

Physical examination including ears/eyes/nose/throat/neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, central and peripheral nervous system, and dermatologic assessments will be performed at the Screening visit. A symptom-directed physical examination, including evaluation of new symptoms and follow-up findings from previous physical examinations, should be performed at each study visit prior to study drug dosing per the Schedule of Assessments.

9.2.5 Height and Weight

Height (cm) should be recorded only at the Screening visit and weight (kg) measurements should be measured per the Schedule of Assessments.

9.2.6 ECOG Performance Status

ECOG performance status will be assessed using the criteria described in **Appendix 1**.

9.2.7 Vital Signs

Vital signs include temperature (ºF/ºC), blood pressure and heart rate.

9.2.8 Laboratory Parameters

The following laboratory parameters will be performed at the indicated time points in the Schedule of Assessments. The Investigator must evaluate all results outside the reference range and determine the clinical significance (clinically significant or not clinically significant) of each result.

- Hematology: hemoglobin, hematocrit, red blood cell count, while blood cell count, neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophil (absolute), mean corpuscular volume and platelet count
- Coagulation tests: INR or PT and PTT (APTT acceptable).
- Serum chemistries: albumin, ALT, AST, alkaline phosphatase, bicarbonate, total bilirubin, blood urea nitrogen, urea, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), sodium, potassium, phosphorus and magnesium.
- Urinalysis: dipstick with micro-analysis if clinically indicated. From the urine sample collected for standard urinalysis assessment, quantitative biochemical analyses of urinary protein, albumin and creatinine is required along with the reporting of the protein:creatinine ratio and the albumin:creatinine ratio. The quantitative analysis of glucose will also be required if quantification can be performed by the local laboratory.
- Calculated creatinine: To be calculated using the Cockcroft-Gault formula.
- Pregnancy test: A serum or urine pregnancy test is required at screening in all women of child-bearing potential. A urine pregnancy test is required at timepoints during the study as indicated in the Schedule of Assessments. A serum pregnancy test will be required if the urine pregnancy test is positive.

9.2.9 12-lead ECG

Twelve-lead ECGs will be obtained at the indicated time points in the protocol and Schedule of Assessments. Triplicate ECGs are to be collected if QTc > 500 msec. QTc is to be measured using the Fridericia correction formula.

9.2.10 Pharmacokinetic (PK) Sampling

Plasma samples will be collected to assess the PK properties of ZEN003694, the metabolite ZEN003791, and talazoparib at the indicated time points in the protocol (**Table 1** and Section **9.1**). Plasma concentrations will be determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method. Samples will be collected as indicated in the Schedule of Assessments and the laboratory manual. Pharmacokinetic sampling details (date, dose, dosing time, sample collection times) will be recorded in the eCRF.

9.2.11 Germline BRCA1/2 Mutation Status and Sampling

Blood samples may be collected at screening to determine germline BRCA1/2 (gBRCA) mutation status at the indicated time points in the protocol, Section **9.1**, and the **Table 1**. The test performed prospectively for patients without gBRCA status will be BRACAnalysis CDx performed by Myriad Genetics. If prior testing of gBRCA status has been performed, reports showing the panel of genes tested to establish BRCA1/2 mutation status are to be deidentified and provided to the Sponsor.

9.2.12 Pharmacodynamic Sampling

- **Whole blood BETi and PARPi PD marker mRNA expression analysis (Part 1 only):** Whole blood will be collected in Cycle 1 to measure the effect of talazoparib on PD marker mRNA expression of BETi responsive genes. RNA will be extracted and mRNA expression of 5 BETi responsive genes, along with a housekeeping control gene (cyclophilin), will be measured using quantitative polymerase chain reaction (qPCR). Possible genes to be analyzed are: [redacted]. Additional genes of interest might be individually tested to correlate with ZEN003694 exposure.

- **Whole Blood ctDNA:** Whole blood will be collected from patients to isolate plasma and the buffy coat for possible future analysis of ctDNA fraction as well as targeted sequencing of the ctDNA for possible correlations with patient's response and tumor biopsies.

- **Tumor Biopsy:** Metastatic tumor biopsies will be taken with core needle or excisional biopsy. Fine needle aspiration is not allowed. It is encouraged that 4 core samples be collected from a single site with a minimum of 2 core samples collected. Biopsies should not be taken from a recent, prior irradiated site. The biopsy samples will be either fixed in formalin and/or frozen for histological and immunohistochemical (IHC) analyses, and RNA and/or DNA sequencing. Samples collected in Part 1 (dose escalation), Part 2 (Simon 2-Stage), and Expansion phase will be banked for possible future analyses of exploratory biomarkers and DDR genes. Possible future analyses of target engagement, changes in gene expression and mutation spectrum that correlate with response of patients to identify potential biomarkers of response to ZEN003694 and talazoparib. IHC will be used to assess candidate markers of DNA damage response to evaluate the impact of ZEN003694 to inhibit homologous recombination and induce DNA damage in combination with talazoparib.

9.2.13 Adverse Events

Adverse events will be collected as defined in Sections **11.1**, **11.2** and **11.3**.

9.2.14 Concomitant Medications

All prior cancer-related treatment and procedures will be captured on the CRFs. All concomitant medications (dose and regimen) taken during the course of the study must be recorded on the Concomitant Medications CRF. In addition, any medications taken 21 days prior to enrollment in the study should be recorded on the Concomitant Medications CRF.

9.2.15 Tumor Assessment – Imaging/Radiologic Evaluation

Tumor assessments are to be performed according to RECIST Version 1.1 guidelines. Whole body imaging (preferably (and if appropriate) by computed tomography (CT)) with cross-sectional imaging of the chest/abdomen/pelvis should be performed in accordance with institutional standards. Use of intravenous contrast is required unless contraindicated. Magnetic resonance imaging (MRI) may be substituted for computed tomography (CT) per the Investigator's discretion.

Bone scans are to be performed if bone metastases are present at time of entry into the study.

Note: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met.

[redacted]

9.2.17 EORTC Quality of Life

A validated quality of life questionnaire (EORTC QLQ-C30, Version 3.0) will be used to evaluate patient reported outcomes to assess the quality of life of cancer patients. An additional supplemental quality of life questionnaire specific to breast cancer (EORTC QLQ-BR23) will also be used to assess specific symptoms related to breast cancer.

10. WITHDRAWAL OR EARLY TERMINATION OF PATIENTS

Patients are free to withdraw from study participation at any time for any reason. Patients may discontinue treatment with ZEN003694 and talazoparib either at their request, at the discretion of the Investigator for medically indicated reasons or for protocol noncompliance. Discontinuation of one drug (either ZEN003694 or talazoparib) requires the discontinuation of both ZEN003694 and talazoparib.

In the event of early termination, the patient should be instructed to report to the clinic as early as possible but within 1 week after the decision to terminate from the study has been made or for the next scheduled clinic visit. All End of Treatment visit procedures (see Section **9.1.6**) and all Safety Follow-up visit procedures (see Section **9.1.7**) are to be conducted. The Investigator shall make his or her best efforts to perform these procedures. The Investigator should make all attempts to accurately identify the reason a patient withdrew from the study, while respecting the patient's privacy. The primary reason for the patient discontinuation should be documented as one of the following:

- Radiographic progression
- Clinical progression
- DLT
- Adverse event
- Treatment with or need for prohibited concomitant medication
- Withdrawal by patient
- Withdrawal by physician
- Non-compliance
- Lost to follow-up
- Death

11. SAFETY ASSESSMENTS

Safety parameters monitored and recorded during this study include, physical examination findings, weight, vital signs, ECOG performance status, ECGs, AEs, laboratory variables (hematology, serum chemistries, coagulation tests and urinalysis).

11.1 Adverse Event and Suspected Unexpected Serious Adverse Reaction Definitions

11.1.1 Adverse Event

An AE is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a pharmaceutical product (i.e., study drug), whether or not considered related to the pharmaceutical product.

The recording of AEs will begin at the start of the administration of the first dose of ZEN003694 and talazoparib. AEs should record the development of an undesirable medical condition, worsening of a pre-existing medical condition and any change in severity (increase or decrease) of a previously recorded AE, during or following exposure to study drug, regardless of relationship to study drug. See Section **11.3** for additional information.

11.1.2 Serious Adverse Event

A serious adverse event (SAE) is any AE that:

- Results in death
- Is life-threatening
    - A life-threatening SAE is any AE that places the patient at immediate risk of death from the reaction as it occurred, as assessed by the Investigator. This definition does not include a reaction that might have caused death if it occurred in a more severe form.
- Requires in-patient hospitalization or prolongs existing hospitalization
    - For the purposes of this protocol, any hospital admission will be considered an in-patient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalizations for a procedure scheduled before study enrollment (first dose of study drug) or elective procedures scheduled during the study. However, unexpected complications that occur during elective surgery should be recorded as AEs and assessed for seriousness.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Is any other important medical event

- Other medical events may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes in the SAE definition. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization of the patient, or the development of drug dependency or drug abuse.

11.1.3 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the study drug and the AE (e.g., assessed as possibly or probably related), and which is both unexpected and serious. An unexpected adverse reaction (i.e., any untoward and unintended response to the study drug) is one for which the nature and severity is inconsistent with the applicable reference safety information (e.g., Investigator's Brochure).

11.2 Reporting Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

Report all SAEs (regardless of drug relatedness) and SUSARs to Drug Safety **WITHIN 24 HOURS** of discovery or notification. Reporting to Drug Safety can be performed by one of two methods: Either complete the SAE eCRF form (preferable method) or record event information on the SAE Report Form, and submit the completed form with any other available pertinent information (e.g., hospital records, laboratory results, etc.) to Drug Safety (contact information are provided in the study reference manual).

The minimum required information for an initial report is:

- Reporter's name and contact information
- Protocol number
- Site and patient identification information
- Event term(s) (with a brief summary of the event[s] and causality assessment)

If additional follow-up information is required or becomes available for a previously reported SAE or SUSAR, the additional information should be entered into the database. Additional new information may also be recorded on a follow-up SAE Report Form and submitted **WITHIN 24 HOURS** from the time the additional information was obtained.

For hospitalizations, all attempts to obtain the hospital record should be documented in the study file. Complete an SAE Report Form with any known information on the hospitalization, however minimal, and submit it to Drug Safety (detailed contact information is provided in the study reference manual).

11.2.1 Disease-related Events That Are Endpoints

For the purposes of this study, progression of the patient's underlying disease ("disease progression") should generally not be reported as an AE or SAE. Any 'symptoms' of disease

progression however should be reported as AEs/SAEs. If however the Investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, the event should be immediately reported to Drug Safety and recorded as an AE or SAE.

Any event that results in death is to be reported as an SAE. Death is an outcome of an adverse event and not an adverse event in itself. The underlying event leading to death is reported as the SAE.

11.3 Adverse Events

Events that occur before the first administration of study drug are not considered AEs, by definition (Section **11.1.1**); record these events on the Medical History CRF.

The Investigator or a qualified designee will question and examine patients for evidence of AEs. Patients should not be asked about specific AEs. Instead, they should be asked general questions (e.g. "How have you been feeling since your last visit?"). Record all AEs on the AE CRF. If a previously reported AE changes in severity, record the change in the AE severity on the AE CRF.

For an event to be recorded as an AE, the onset must occur during or after the patient's first exposure to study drug and no later than 30 days after the last study drug dose. However, there is no limit on reporting SAEs considered reasonably related to ZEN003694. Immediately report all SAEs and deaths to Drug Safety **(**Section **11.2**). This requirement includes deaths within 30 days of the last dose of study drug, or before the last formal follow-up contact, whichever occurs later. The Investigator should follow all AEs that are considered reasonably related to study drug until resolution or stabilization. All other AEs should be followed until resolution or stabilization or until the final visit, whichever occurs first.

Record syndromes rather than individual signs or symptoms in order to avoid double reporting of events and facilitate meaningful interpretation of data. For example, a patient presenting with rhinitis, fever, and headache should be reported as having "flu-like symptoms," without independently recording each accompanying sign. When no clearly recognizable clinical syndrome can be described, record individual clinical signs and symptoms.

All AEs that occur during the study should be treated appropriately to protect and ensure the patient's well-being. If such treatment constitutes a deviation from this protocol, Drug Safety must be notified and the Investigator should comply with applicable Ethics Committee (EC) or Institutional Review Board (IRB) reporting requirements.

The Investigator is responsible for determining whether or not an AE is severe enough to require the patient's removal from treatment. A patient may also voluntarily withdraw from treatment because of an AE. If either occurs, the patient must receive appropriate medical care, and the Investigator must strongly encourage the patient to return to the study site for the final protocol-specified visits and assessments, and to continue returning to the study site for follow-up evaluations until the AE resolves or stabilizes. All AEs, serious or not, that result in permanent withdrawal from the study treatment should be immediately reported to Drug Safety.

The Sponsor will conduct reviews of all available AEs approximately once every 3 months. During dose escalation, these review timelines may be modified to coincide with enrollment and

dose-escalation safety data. The study sites are to ensure timely entry of AEs on the CRFs to facilitate these reviews.

11.3.1 Commonly reported Study Drug Related Adverse Events

The most common AEs related to ZEN003694 are visual impairment (typically a transitory perception of brighter lights and/or light flashes, with or without visual color tinges, and with no functional consequences), nausea, fatigue, decreased appetite, vomiting, creatinine increase, platelet decrease, diarrhea, dehydration, decreased weight, dizziness, dysgeusia, and thrombocytopenia. AEs most commonly observed with talazoparib are fatigue, nausea, anemia thrombocytopenia, neutropenia, leukopenia, diarrhea, vomiting, headache, alopecia, decreased appetite, abdominal pain, dizziness, and weakness. As the two drugs have overlapping AEs, the assessment of relatedness as attributed to either talazoparib alone or ZEN003694 alone may not be not be possible and for such cases should be reported as attributable to the combination of talazoparib and ZEN003694.

11.3.2 Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE using the NCI CTCAE Version 5.0 (see **Appendix 2**).

It is important to distinguish between AE seriousness and severity; these terms are not interchangeable. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section **11.1.2**.

11.3.3 Classification of Adverse Events by Relationship to Study Drug

For each AE, the Investigator must decide whether there is a reasonable possibility that the event was caused by administration of ZEN003694 (i.e., that the event was a suspected adverse reaction). The Investigator should make this decision after careful consideration of the following questions:

- Does the AE follow a reasonable temporal sequence from administration of study drug?
- Can the AE be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other therapy?
- Do the AE symptoms disappear or decrease on cessation of study drug or reduction in study drug dose? (There are exceptions when an AE does not disappear on discontinuation of the drug, yet drug relatedness clearly exists [e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.]).
- Does the AE reappear or worsen when the study drug is re-administered?
- Does the AE follow an expected response pattern based on the established pharmacologic and toxicologic effects of the study drug?
- Does the AE follow an expected response pattern based on the known effects of other products in the same class?

For this assessment, the Investigator will classify each AE as one of the following:

- **Yes, Related:** The AE is definitely related or even considered possibly or probably related to study drug administration.
- **Not Related:** The AE is clearly due to other causes (e.g. concurrent medication, underlying disease, etc.).

11.4 Abnormal Laboratory Results

Abnormal laboratory results may occur in the context of an AE that is a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or elevated AST/ALT in the setting of an AE of hepatitis). In these cases, do not record the abnormality itself as an AE.

However, in the absence of an AE that encompasses an observed abnormal laboratory result, report the abnormality as an AE if the Investigator judges it to be clinically significant for the patient.

For the purposes of this study, the criteria for a "clinically significant" abnormal laboratory result are any of the following:

- It leads to DLT
- It results in any therapeutic intervention
- It is judged by the Investigator to be of other particular clinical relevance

11.5 Overdose

All study drugs will be administered orally.

There is no data regarding ZEN003694 or talazoparib overdose in humans. An overdose and AEs should be treated as per standard medical practice.

Dosing details should be captured on the Study Drug CRF. If the patient receives a dose of a study drug that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented on the AE CRF and on a SAE form as appropriate. Do not capture the event on the AE CRF or SAE form if the patient is not symptomatic.

Should an overdose occur, the Investigator should also monitor the patient with appropriate blood counts and serum chemistry tests and should also provide supportive therapies as necessary.

11.6 Pregnancy

All female patients of childbearing potential are required to consistently and correctly use a highly effective form of contraception. Highly effective forms of contraception include: combined (estrogen and progestogen hormonal contraceptives (oral, intravaginal, transdermal) associated with inhibition of ovulation; progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence). Males with partners of childbearing potential may be enrolled if they use a condom when having sex with a pregnant woman or with a non-pregnant female of childbearing potential from 21 days before the first dose of study drug through 4 months after the last dose of study drug.

Any female patient who becomes pregnant while on study treatment must be withdrawn from the study. If a female partner of a male patient becomes pregnant, the male patient must immediately notify the Investigator, and the Investigator must then immediately notify the Sponsor, or designee. The female partner must sign an ICF for disclosure of information on the pregnant partner's and baby's health status. Information about the pregnancy of any female patient or female partner of a male patient will be collected on a pregnancy form for a period of 3 months after the date of delivery and will include: demographic data, general health condition, abnormalities and safety events.

11.7 Study Safety Monitoring and Dose Escalation or Modification

The Investigator(s) and Sponsor will review safety and available PK data (e.g., C_{max} and AUC) for each cohort in the dose escalation phase to decide when it is permissible to open a new cohort per the study design described in the protocol. Safety data will include but are not limited to SAEs, AEs and laboratory (protocol specified or ad hoc) data, as well as additional information provided by the treating Investigators. Additionally, the accruing safety data for all patients to date will be included in the decision making process for dose escalation or modification. Dose escalation or modifications will be allowed in the absence of an unreasonable and significant risk of illness or injury to patients. In addition, the Sponsor will review the study safety data on an ongoing basis. An independent specialist may participate in the safety review, if appropriate.

11.8 Reporting Safety Information to the Institutional Review Board

The Sponsor or its designee will provide written safety reports or other safety-related communications to the Investigator. The Investigator will ensure that these reports are reviewed and processed in accordance with regulatory and EC/IRB requirements and archived in the site's study file.

At the completion or early termination of the study, the Investigator will submit a final report to the EC/IRB in accordance with local requirements.

12. STUDY ENDPOINTS

12.1 Primary Endpoints

Part 1:

- Safety profile of ZEN003694 in combination with talazoparib
- DLT characteristics and MTD determination for ZEN003694 in combination with talazoparib
- RP2D of ZEN003694 in combination with talazoparib for further clinical investigation

Part 2:

- Clinical benefit rate (CBR) defined as a complete response (CR), partial response (PR) or stable disease (SD $\geq$ 4 cycles) by RECIST v1.1

Expansion Cohort A (Combination Treatment in post-TROP2-ADC patients):

- Objective response rate (ORR) by RECIST v1.1 (CR or PR) by investigator and by independent review

12.2 Secondary Endpoints

Part 1:

- Plasma concentrations of ZEN003694, the active metabolite ZEN003791 and talazoparib. The following PK parameters, at a minimum, will be calculated as appropriate: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, C_{max} and minimum or trough concentration (C_{min}), dosing interval, and T_{max} and half-life ($t_{1/2}$)
- Clinical benefit rate (CBR)
- Overall response rate (ORR)
- Progression-free survival (PFS)
- Quality of Life

Part 2:

- Progression-free survival (PFS)
- Objective response rate (ORR)
- Duration of response (DOR)
- Plasma concentrations of ZEN003694, the active metabolite ZEN003791 and talazoparib. The following PK parameters, at a minimum, will be calculated as appropriate: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$, C_{max} and minimum or trough concentration (C_{min}), dosing interval, and T_{max} and half-life ($t_{1/2}$)
- Quality of Life
- Safety

Expansion Cohort A: Combination Treatment (post-TROP2-ADC patients)

- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression free survival (PFS)
- Safety analyses will include, but are not limited to, AEs, laboratory abnormalities, ECG evaluations, and vital signs
- Pharmacokinetics: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$,, Cmax, Cmin, Tmax, and T½ of ZEN003694, ZEN003791, and talazoparib during the first 2 treatment cycles
- Quality of Life

Expansion Cohort B: ZEN003694 Monotherapy

In discussions with the FDA, if there are 1 or 0 patients (out of the 10 evaluable patients enrolled) who show an objective response to ZEN003694 monotherapy, it could be concluded that ZEN003694 as a monotherapy has no clinical benefit.

Expansion Cohort C: Combination Treatment (TROP2-ADC-naïve patients)

- Objective response rate (ORR) by RECIST v1.1 (CR or PR) by investigator
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression free survival (PFS)
- Safety analyses will include, but are not limited to, AEs, laboratory abnormalities, ECG evaluations, and vital signs
- Pharmacokinetics: $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$,, Cmax, Cmin, Tmax, and T½ of ZEN003694, ZEN003791, and talazoparib during the first 2 treatment cycles
- Quality of Life

12.3 Exploratory Endpoints

Part 1 only:

- Modulation of PD marker mRNA expression by BETi and PARPi

Parts 1 and 2, and Expansion Cohorts:

Possible analysis of:

- RNA-sequencing, and/or DNA-sequencing and candidate protein markers by IHC in tumor tissue
- Targeted DNA sequencing of ctDNA and determination of ctDNA fraction.

13. STATISTICS

13.1 General Considerations

The primary statistical analysis of the data will be descriptive in nature. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by patient counts and related percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

Based on the characteristics of the study design and lack of a concurrent control arm, formal testing of treatment effects (i.e., inferential statistics) will not be performed. However, some measures will be summarized by both point estimates and the associated 95% confidence intervals.

Retrospective analysis of pharmacodynamic assessments for somatic BRCA1/2 mutations and analysis of outcomes for patients with prior platinum therapies may be performed.

13.2 Sample Size Determination

Part 1: Dose escalation

A conventional algorithm (3+3 patients per dose level) will be used to identify the MTD, escalating on 0 of 3 or 1 of 6 DLTs, and de-escalating if 2 DLTs are encountered. The MTD will be the highest dose level at which 0 of 3 or 1 of 6 patients experience a DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT. With this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20%, and less than 50% chance of escalation if the true but unknown rate of DLT is higher than 30%.

Approximately 12 patients will be enrolled in the dose escalation phase of the study.

Part 2: Simon 2-Stage

- The null hypothesis that the true clinical benefit rate (CBR) is 20 % will be tested against a one-sided alternative. (CBR of 20% is not of clinical interest whereas CBR 40% warrants further investigation)
- In the first stage, 17 patients will be accrued. If there are < 4 patients with clinical benefit in these 17 patients, the study will be stopped.
- Otherwise, 20 additional patients will be accrued for a total of 37. The null hypothesis will be rejected if 11 or more patients show clinical benefit out of 37 patients.
- This design yields a type I error rate of 0.1 when the true CBR is 20% and power of 90% when the true CBR is 40% (target error rates 0.10 and 0.10); the probability of early termination is 0.55.
- A minimum of 17 and a maximum of 37 evaluable patients will be accrued.

- ORR will be reported with 90% CI. AEs will be summarized. PFS and duration of response will be summarized with Kaplan-Meier curves. Clinical benefit rate will be reported with 90% CI.

Expansion Cohort A: Combination Treatment (post-TROP2-ADC patients):

The expansion combination treatment cohort will enroll patients with locally advanced or metastatic TNBC without germline BRCA1/BRCA2 mutations who have had prior treatment with sacituzumab govitecan and have had at least one additional prior systemic therapy for locally advanced or metastatic disease. Approximately 80 evaluable patients are planned to establish the ORR and further define the safety profile of the combination ZEN003694 + talazoparib. An observed ORR (by blinded independent central review) of at least 30% represents a significant improvement over current available therapies in this patient population. With 80 patients, 24 or more responders will provide an observed ORR of at least 30% and a lower limit of the 95% confidence interval above 20%. The RECIST v1.1 assessment of response will be assessed by an independent central review committee.

Expansion Cohort B: ZEN003694 Monotherapy:

Expansion Cohort B will enroll patients with locally advanced or metastatic TNBC without germline BRCA1/BRCA2 mutations who have had two prior systemic treatments for locally advanced or metastatic disease. Approximately 10 evaluable patients are planned to assess the anti-tumor activity of ZEN003694 monotherapy. According to FDA discussions, if no more than 1 patient has a confirmed objective response (complete response or partial response), it can be concluded that ZEN003694 monotherapy does not have anti-tumor activity (clinical benefit) when given as a single drug treatment.

Expansion Cohort C: Combination Treatment (TROP2-ADC-naive patients)

Expansion Cohort C will enroll patients with locally advanced or metastatic TNBC without germline BRCA1/BRCA2 mutations who have not previously received sacituzumab govitecan and have had at least two additional prior systemic therapies for locally advanced or metastatic disease. Approximately 30 evaluable patients are planned to establish the ORR and further define the safety profile of the combination ZEN003694 and talazoparib.

13.3 Analysis Populations

Safety population: Patients who receive at least one dose of ZEN003694.

Efficacy population: Patients enrolled in Part 2 and Expansion who receive at least one dose of ZEN003694 and talazoparib.

13.4 Data Handling

Clinical data will be entered into a secure clinical database that it is Part 11 compliant. The handling of data, including data quality assurance, will comply with regulatory guidelines, and

will be defined in a study-specific data management plan (DMP). The DMP will define roles and responsibilities in regard to data management, data quality processes and expectations, from study start-up to final database lock.

13.5 Statistical Analyses

Prior to the analysis of the final study data, a detailed statistical analysis plan (SAP) will be written. Detailed information regarding analysis datasets, summarization of the data and analyses will be provided in the SAP. The SAP will contain any modifications to the analyses described in this section.

14. QUALITY CONTROL AND QUALITY ASSURANCE

Prior to participation in this study, investigational sites and Investigators will be evaluated for appropriate qualifications and ability to properly execute the study. Each investigational site must undergo proper training on the study protocol and ancillary study procedures/documents through participation in an initiation visit or Investigator meeting. Such training must take place before any patients are enrolled at that site. Initiation visits and Investigator meetings will include but may not be limited to review of Good Clinical Practice (GCP) guidelines, study drug procedures, data collection requirements and patient eligibility requirements.

The Sponsor or designee will make periodic visits to the investigational site to assess compliance with study procedures and regulatory requirements; to ensure that the safety, welfare and privacy of patients are being protected; and to verify the accuracy and integrity of the study data.

In addition, the Sponsor will periodically review the study data to ensure that data are being appropriately collected and reported. Logic checks will be also programmed and run to identify errors and data discrepancies. Discrepancies will be reviewed with investigational site personnel, corrections will be made to the database, and a validated audit trail will be maintained. The database will be locked and audited before it is released for analysis.

14.1 Study Monitoring

Before the initiation of the study, a representative from the Sponsor will visit the investigational site to:

- Determine the adequacy of the facilities
- Discuss the responsibilities of the Investigator(s) and other personnel involved with the study with regard to protocol adherence and the responsibilities of the Sponsor and their representatives

During the study, the Study Monitor will have regular contact with the investigational site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded on the CRFs, and that the investigational product accountability is being performed.
- Perform source data verification (a comparison of the data on the CRFs with the patient's records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient e.g., clinic charts. Incorrect or missing entries on to the CRFs will be queried and must be corrected immediately.

14.2 Audit and Inspection

During or after the study is completed, the Sponsor, its representatives or a Regulatory Authority may wish to carry out an audit or inspection. These representatives must have the same access to study data and patient source data as the Study Monitor.

14.3 Regulatory Authority Correspondence

The Investigator will notify the Sponsor or designee immediately following any regulatory contact with the investigational site. The Investigator will provide requested copies of all correspondence with the Regulatory Authority that may affect the review of the current study (e.g., Form 483, Inspectional Observations). The Sponsor or their designee reserves the right to be at the investigational site during any regulatory inspection that involves this protocol.

15. ETHICAL AND LEGAL ISSUES

15.1 Statement of Compliance

This study will be conducted in accordance with the following:

- Protocol-related and study-related documents
- GCP as outlined in the International Conference on Harmonization (ICH) E6 guideline and regional regulations
- Regional required patient data protection laws and regulations
- Applicable regional regulations

15.2 Ethics Committee or Institutional Review Board Approval

The Principal Investigator at each site is responsible for obtaining regional EC or IRB approval for the final protocol, the Sponsor-approved ICF/assent, patient information sheet, if applicable, and any advertisements to recruit patients. Written approval of these documents must be obtained from the EC/IRB and a copy submitted to the Sponsor before any patient is enrolled at an investigational site.

The Principal Investigator is also responsible for the following interactions with the regional EC/IRB.

- Obtaining EC/IRB approval for any protocol amendments and ICF/assent revisions before implementing the changes
- Providing the EC/IRB with any required information before or during the study
- Submitting progress reports to the EC/IRB as required during the conduct of the study, requesting re-review and approval of the study as needed, and providing copies of all EC/IRB renewal of approvals and relevant communication to the Sponsor and/or its representative
- Notifying the EC/IRB of all serious and unexpected AEs related to the study medication reported by the Sponsor and/or its representative, as required
- Notifying the EC/IRB at the end of the study, in accordance with regional guidelines and regulations

15.3 Patient Informed Consent/Assent

The Investigator's draft ICF/assent must be reviewed by the Sponsor and/or its representative prior to submission to a regional EC/IRB for approval. A copy of the ICF/assent approved by the EC/IRB must be forwarded to the Sponsor and/or its representative.

The consent of the patient to participate in the study has to be given in writing prior to enrollment. It must be signed and personally dated by the patient, parent, legal guardian or caretaker and by

the Investigator, Sub-investigator or study coordinator designated by the Investigator to conduct the informed consent discussion. The signed and dated declaration of informed consent will remain at the Investigators' site and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated ICF should be provided to the patient prior to participation and the original maintained in the patient's source documents or in a separate archive file for the informed consent documents for the study.

15.4 Patient Compensation for Adverse Effects on Health

The Sponsor and/or its representative will adhere to regional regulations regarding clinical trial compensation to patients whose health is adversely affected by participation in the study.

15.5 Changes to the Conduct of the Study, Protocol and Study Termination

15.5.1 Protocol Amendments

Changes in the study protocol shall be in the form of written study protocol amendments. These will require the approval of all signatories of the final protocol. Any substantial amendments to the protocol that affect the patient, e.g., changes in procedures/assessments or matters relating to patient safety, require a favorable opinion from the EC/IRB for the study sites prior to implementation. Changes of a purely administrative nature should be notified to the committee(s) as applicable, but do not require formal approval. However, a change to the protocol to eliminate an apparent immediate hazard to the patient may be implemented immediately provided the EC/IRB and applicable Regulatory Authorities are subsequently notified by protocol amendment. Any amendment affecting the patient requires further informed consent from each patient before implementation.

15.5.2 Study Termination

The Sponsor reserves the right to terminate the study at any time for any reason. The Investigator should notify the EC/IRB in writing of the completion or early termination of the study. The Sponsor will promptly notify US FDA and other Regulatory Authorities if enrollment is terminated or suspended for any reason. Upon study completion or termination, applicable regulatory reporting requirements will be followed.

16. INVESTIGATOR RESPONSIBILITIES

The Investigators shall be responsible for ensuring that the study is performed in accordance with the protocol, Food and Drug Administration (FDA)/ICH GCP regulations and applicable regional regulatory requirements.

16.1 Staff Training

The Investigator will maintain a record of all individuals involved in the study. He or she will ensure that appropriate training relevant to the study is given to all staff members involved in this study, and that they will receive any new information of relevance to the performance of this study. The Investigator should maintain a list of appropriately trained persons to whom the Investigator has delegated trial-related duties.

16.2 Study Conduct

In signing this protocol, the Investigator agrees to:

- Conduct the study in accordance with the relevant, current protocol and make changes only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human patients
- Comply with the ICH guidelines on GCPs plus appropriate regional regulatory laws and requirements
- Personally conduct or supervise the described investigation
- Inform any patients or persons used as controls that the study drugs are being used for investigational purposes
- Ensure requirements relating to obtaining informed consent and EC or IRB approval have been met
- Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Section **11**
- Read and understand the Investigator's Brochure, including potential risks and side effects of the drug
- Ensure all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting their commitments
- Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative, or any regulatory agency authorized by law
- Promptly report to the EC or IRB all changes in research activity and all unanticipated problems involving risks to human patients or others
- Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements

- Administer study drug only to patients who meet study entry criteria and are enrolled in the study, and only according to the guidelines set forth in this protocol

16.3 Recordkeeping

The Investigator is responsible for maintaining adequate records to fully document the conduct of the study, including but not limited to the following:

- All versions of the Investigator's Brochure and the signed protocol and amendments in effect during the conduct of the study
- Signed ICFs/assents
- Source documents including adequate case histories
- Signed, dated and completed CRFs or data collection forms and documentation of data corrections
- Notification of SAEs and related reports
- Investigational product accountability logs and documentation of return of unused and used investigational product, if applicable
- Dated and documented EC/IRB approvals
- Normal laboratory test values and laboratory certifications, if applicable
- Curricula vitae of all clinical Investigators
- Completed Forms US FDA 1572
- Trial initiation documentation
- Delegation of Authority Log
- Signed Signature of Agreement for Protocol and Amendment and agreements between involved parties
- Relevant communication, including that related to the Study Monitor's site visits (e.g., letters, meeting notes, notes from telephone calls)
- Interim, annual or final reports to ECs/IRBs
- Patient screening log, patient identification code list and patient enrollment log
- Audit certificate if applicable

17. PUBLICATIONS

The data and information generated in this study are the exclusive property of the Sponsor and Pfizer and are confidential.

To avoid disclosures that could jeopardize proprietary rights, the investigator agrees to give the Sponsor and Pfizer the right to review all manuscripts, abstracts, and presentations related to this study at least 30 days *prior* to their submission for publication or presentation. Authorship among Investigators generally will be based on the extent of significant contribution, including scientific and clinical, to the publication.

18. CONFIDENTIALITY

The Investigators as well as their staff, and all its representatives must agree to maintain the confidentiality of the study at all times and must not reveal information relating to the Investigator's Brochure, protocol, CRFs or associated documents to unauthorized third parties.

19. REFERENCES

Aftimos P, Bechter O, Awada A, Jungels C, Dumez H, Huyvaert N, Costermans J, Lee C, Meeus MA, Burkard U, Musa H, Zhao Y, Schoffski P. Phase I first-in-man trial of a novel bromodomain and extra-terminal domain (BET) inhibitor (BI 894999) in patients (Pts) with advanced solid tumors. J Clin Oncol 35, 2017 (suppl; abstr 2504)

Amé JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, et al. (1999) PARP 2, a novel mammalian DNA damage dependent poly(ADP ribose) polymerase. *J Biol Chem.* 1999 Jun 18;274(25):17860 8

Bareche Y, Venet D, Ignatiadis M, Aftimos P, Piccart M, Rothe F, Sotiriou C. Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis. Ann Oncol. 2018 Jan 22

Basch, E., Prestrud, A. A., Hesketh, P. J., Kris, M. G., Feyer, P. C., Somerfield, M. R., . . . American Society of Clinical, O. (2011). Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol, 29*(31), 4189-4198. doi: 10.1200/JCO.2010.34.4614

Bauer, KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 May 1;109(9):1721-8

Berthon C, Raffoux E, Thomas X, Vey N, Gomez-Roca C, Yee K, Taussig DC, Rezai K, Roumier C, Herait P, Kahatt C, Quesnel B, Michallet M, Recher C, Lokiec F, Preudhomme C, Dombret H. Bromodomain inhibitor OTX015 in patients with acute leukaemia: a dose-escalation, phase 1 study. Lancet Haematol. 2016 Apr;3(4):e186-95

Bryant, H.E., Schultz, N., Thomas, H.D., Parker, K.M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N.J., Helleday, T. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. (2005) *Nature* 434:913-916.

Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, Altman DG, Eccles B, Gerty S, Durcan LT, Jones L, Evans DG, Thompson AM, Pharoah P, Easton DF, Dunning AM, Hanby A, Lakhani S, Eeles R, Gilbert FJ, Hamed H, Hodgson S, Simmonds P, Stanton L, Eccles DM. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018 Feb;19(2):169-180. doi: 10.1016/S1470-2045(17)30891-4

Curtin, N.J. PARP inhibitors for cancer therapy. (2005) *Expert Rev Mol Med.* 2005 Mar 15;7(4):1 20

Dawson, M. A., Kouzarides, T., & Huntly, B. J. (2012). Targeting epigenetic readers in cancer. *The New England journal of medicine, 367*(7), 647-657. doi: 10.1056/NEJMra1112635

Dawson, M. A., Prinjha, R. K., Dittmann, A., Giotopoulos, G., Bantscheff, M., Chan, W. I., . . . Kouzarides, T. (2011). Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. *Nature, 478*(7370), 529-533. doi: 10.1038/nature10509

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., . . . Verweij, J. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer, 45*(2), 228-247. doi: 10.1016/j.ejca.2008.10.026

Farmer, H., McCage, N., Lord, C.J., Tutt, A.N.J., Johnson, D.A., Richardson, T.B., Santarosa, M., Dillon, K.J., Hickson, I., Knights, C., Martin, N.M.B., Jackson, S.P., Smith, G.C.M., Ashworth, A. (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 434:917-920

Filippakopoulos, P., & Knapp, S. (2014). Targeting bromodomains: epigenetic readers of lysine acetylation. *Nat Rev Drug Discov, 13*(5), 337-356. doi: 10.1038/nrd4286

Gibson BA, Kraus WL. (2012) New insights into the molecular and cellular functions of poly(ADP ribose) and PARPs. *Nat Rev Mol Cell Biol.* 2012 Jun 20;13(7):411-24

Goodell, M. A., & Godley, L. A. (2013). Perspectives and future directions for epigenetics in hematology. *Blood, 121*(26), 5131-5137. doi: 10.1182/blood-2013-04-427724

Goodin S, Griffith N, Chen B, et al. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. *Journal of Oncology Practice*. American Society of Clinical Oncology 2011;7:7-12.

Hnisz, D., Abraham, B. J., Lee, T. I., Lau, A., Saint-Andre, V., Sigova, A. A., . . . Young, R. A. (2013). Super-enhancers in the control of cell identity and disease. *Cell, 155*(4), 934-947. doi: 10.1016/j.cell.2013.09.053

Hopkins TA, Shi Y, Rodriguez LE, Solomon LR, Donawho CK, DiGiammarino EL, et al. (2015) Mechanistic dissection of PARP1 trapping and the impact on in vivo tolerability and efficacy of PARP inhibitors. *Mol Cancer Res.* 2015 Nov;13(11):1465 77

Johansson M. (1999) A human poly(ADP ribose) polymerase gene family (ADPRTL): cDNA cloning of two novel poly(ADP ribose) polymerase homologues. *Genomics* 1999 May 1;57(3):442 5

Karakashev S, Zhu H, Yokoyama Y, Zhao B, Fatkhutdinov N, Kossenkov AV, Wilson AJ, Simpkins F, Speicher D, Khabele D, Bitler BG, Zhang R. (2017) BET Bromodomain Inhibition Synergizes with PARP Inhibitor in Epithelial Ovarian Cancer. *Cell Rep*. 2017 Dec 19;21(12):3398-3405

Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, Fralick M, Kumar R, Clemons M. (2009) Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. *Clin Breast Cancer*. 2009 Feb;9(1):29-33

Litton J, Rugo HS, Ettl J, Hurvitz S, Gonçalves A, Lee K-H, Fehrenbacher L, Yerushalmi R, Mina LA, Martin M, Roché H, Im Y-H, Quek RGW, Tudor IC, Hannah AL, Eiermann W, Blum JL. (2018) Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 379, 753-763

Lord, C.J., and Ashworth, A. (2017) PARP inhibitors: Synthetic lethality in the clinic. *Science* 355, 1152-1158

Loven, J., Hoke, H. A., Lin, C. Y., Lau, A., Orlando, D. A., Vakoc, C. R., . . . Young, R. A. (2013). Selective inhibition of tumor oncogenes by disruption of super-enhancers. *Cell,* 153(2), 320-334. doi: 10.1016/j.cell.2013.03.036

McCabe, N., Turner, N.C., Lord, C.J., Kluzek, K., Bialkowska, A., Swift, S., Giavara, S., O'Connor, M.J., Tutt, A.N., Zdzienicka, M.Z., Smith, G.C.M., Ashworth, A. (2006) Deficiency in the Repair of DNA Damage by Homologous Recombination and Sensitivity to Poly(ADP-Ribose) Polymerase Inhibition. *Cancer Res* 66:(16), 8109-8115

Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. (2012) Trapping of PARP1and PARP2 by clinical PARP inhibitors. *Cancer Res*. Nov 1;72(21):5588-99

Murai J, Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, et al. (2014) Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol Cancer Ther* 13:433–43

Neff, T., & Armstrong, S. A. (2013). Recent progress toward epigenetic therapies: the example of mixed lineage leukemia. *Blood, 121*(24), 4847-4853.

Oken, MM, Creech, RH, Tormey, DC, et al., (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am. J. Clin. Oncol.* 5(6):649-655.

O'Shaughnessy J, Schwartzberg L, Danso MA, Miller KD, Rugo HS, Neubauer M, Robert N, Hellerstedt B, Saleh M, Richards P, Specht JM, Yardley DA, Carlson RW, Finn RS, Charpentier E, Garcia-Ribas I, Winer EP. (2014) Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J Clin Oncol.* 32(34):3840-7

Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Delaloge S, Li W, Tung N, Armstrong A, Wu W, Goessl C, Runswick S, Conte P. (2017) Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med.* 377(6):523-533

Schreiber, V, Amé JC, Dollé P, Schultz I, Rinaldi B, Fraulob V, et al. (2002) Poly(ADP ribose) polymerase 2 (PARP 2) is required for efficient base excision DNA repair in association with PARP 1 and XRCC1. J Biol Chem. 2002 Jun 21;277(25):23028 36

Schrieber, V., Dantzer, F., Ame, J.C., de Murcia, G. (2006) Poly (ADP ribose): Novel functions for an old molecule. *Nat. Rev. Mol. Cell. Biol.* Jul; 7(7):517-528.

Shi, J., & Vakoc, C. R. (2014). The mechanisms behind the therapeutic activity of BET bromodomain inhibition. *Molecular cell, 54*(5), 728-736. doi: 10.1016/j.molcel.2014.05.016

Simon, R. (1989) Optimal Two-Stage Designs for Phase II Clinical Trials. *Controlled Clinical Trials* 10:1-10

Smith, T. J., Bohlke, K., Lyman, G. H., Carson, K. R., Crawford, J., Cross, S. J., . . . Armitage, J. O. (2015). Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol, 33*(28), 3199-3212. doi: 10.1200/JCO.2015.62.3488

Stathis A, Zucca E, Bekradda M, Gomez-Roca C, Delord JP, de La Motte Rouge T, Uro-Coste E, de Braud F, Pelosi G, French CA. (2016) Clinical Response of Carcinomas Harboring the BRD4-NUT Oncoprotein to the Targeted Bromodomain Inhibitor OTX015/MK-8628. *Cancer Discov*. 6(5):492-500

Sun C, Yin J, Fang Y, Chen J, Jeong KJ, Chen X, Vellano CP, Ju Z, Zhao W, Zhang D, Lu Y, Meric-Bernstam F, Yap TA, Hattersley M, O'Connor MJ, Chen H, Fawell S, Lin SY, Peng G, Mills GB. (2018) BRD4 Inhibition Is Synthetic Lethal with PARP Inhibitors through the Induction of Homologous Recombination Deficiency. *Cancer Cell.* 33(3):401-416.e8

Tsujikawa L, Norek K, Calosing C, Attwell S, Gilham D, Sharma N, Tobin J, Haager M, Jahagirdar R, Lakhotia S. (2017) AACR Abstract LB-038: Pre-clinical development and clinical validation of a whole blood pharmacodynamic marker assay for the BET bromodomain inhibitor ZEN003694 in metastatic castration-resistant prostate cancer (mCRPC) patients. *Cancer Res* 77: LB-038-LB-038

Turner, N.C., Telli, M.L., Rugo, H.S., Mailliez, A., Ettl, J., Grischke, E.-M., Mina, L.A., Gelpi, J.B., Fasching, P.A., Hurvitz, S.A.*, et al.* (2017). Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO). *Journal of Clinical Oncology 35*, 1007-1007

Wilson, A.J., Stubbs, M., Liu, P., Ruggeri, B., Khabele, D. (2018) The BET inhibitor INCB054329 reduces homologous recombinatin efficiency and augments PARP inhibitor activity in ovarian cancer. *Gynecologic Oncology* 149:575-584. https://doi.org/10.1016/j.ygyno.2018.03.049.

Wyatt, A. W., Annala, M., Aggarwal, R., Beja, K., Feng, F., Youngren, J., . . . Gleave, M. E. (2017). Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer. *Journal of the National Cancer Institute, 109*(12). doi:10.1093/jnci/djx118

Wyatt, A. W., Azad, A. A., Volik, S. V., Annala, M., Beja, K., McConeghy, B., . . . Chi, K. N. (2016). Genomic Alterations in Cell-Free DNA and Enzalutamide Resistance in Castration-Resistant Prostate Cancer. *JAMA Oncol*. doi:10.1001/jamaoncol.2016.0494

Wyatt, A. W., & Gleave, M. E. (2015). Targeting the adaptive molecular landscape of castration-resistant prostate cancer. *EMBO Mol Med, 7*(7), 878-894. doi: 10.15252/emmm.201303701

Yang L, Zhang Y, Shan W, Hu Z, Yuan J, Pi J, Wang Y, Fan L, Tang Z, Li C, Hu X, Tanyi JL, Fan Y, Huang Q, Montone K, Dang CV, Zhang L. (2017) Repression of BET activity sensitizes homologous recombination-proficient cancers to PARP inhibition. *Sci Transl Med* 26:9(400)

Zuber, J., Shi, J., Wang, E., Rappaport, A. R., Herrmann, H., Sison, E. A., . . . Vakoc, C. R. (2011). RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia. *Nature, 478*(7370), 524-528. doi: 10.1038/nature10334

Appendix 1: ECOG Performance Status

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

Source: **Oken, et al., 1982**

Appendix 2: NCI CTCAE Version 5.0 Adverse Event Severity Grading

Grade refers to the severity of the AE. The NCI CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline as shown in the table below.

Adverse Event Severity Grading — NCI CTCAE

	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semicolon (;) indicates "or" within the description of the grade. A single dash (–) indicates a grade is not available. Not all grades are appropriate for all AEs; therefore, some AEs are listed with fewer than 5 options for grade selection.

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Appendix 3: RECIST 1.1 Criteria

MEASUREMENT OF RESPONSE

Measurement of response in patients with measurable disease

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria (**Eisenhauer et al., 2009**). Changes in the sum of the diameters of target lesions of the tumor lesions are used in the RECIST criteria.

> **Note:** lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Measurable disease/ Target lesions

> All measurable lesions (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded except for target lymph nodes with are measured on the short axis] as ≥ 10mm with spiral CT) up to a maximum of 2 lesions per organ and 5 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and the suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.
>
> Lymph node metastases must measure 1.5 cm or greater in short axis diameter to be considered target lesions, while other target lesions must measure 1 cm or greater (with spiral CT scans).

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including baseline LD), or the appearance of one or more new lesions

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s), and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions

Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started, including baseline; see table below). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum of 12 weeks after study entry.

Duration of overall response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of non-measurable bone disease

Bone scans obtained after the baseline evaluation will be used to evaluate post-treatment changes. Bone scans obtained will be evaluated as either "no new lesions" or "new lesions" on the tumor measurement forms.

a. For the first scheduled reassessment: New lesions at the first scheduled evaluation will require a confirmatory bone scan 6 or more weeks later. If no new lesions are observed on the confirmatory bone scan, study therapy is continued. If additional new lesions are observed, then the patient has experienced progression. Progression in this situation is dated as the time of the first reassessment scan.

b. For subsequent scheduled reassessments: If no new lesions are observed, study therapy will continue. If new lesions are observed, this is evidence of disease progression. Date of progression is the date at which the scan was obtained.

Progressive disease (PD)

Progressive disease will be defined by <u>any one</u> of the following:

a. Appearance of new metastatic lesions outside the bone

b. New metastatic lesions on bone scan confirmed as described above

c. Development of an indication for radiotherapy while on treatment

d. Unequivocal progression of non-target lesions

e. Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression

Appendix 4: Investigator Agreement Page

A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer

Protocol ZEN003694-004
Protocol Amendment 6: 26 May 2022

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. Further, I agree to conduct this study in accordance with ICH Guidelines, all applicable United States (US) Regulations (21 CFR parts 50, 54, 56 and 312) and Good Clinical Practice and applicable regulatory requirements.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from the Sponsors, except to the extent necessary for the conduct of the study at this study site.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the Sponsors. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator's Signature	**Date**

Principal Investigator's Name: (Print) _____

Institution's Name, City, State: _____

_____

_____

Appendix 5: Sponsor Signature Page (China only)

Protocol #	ZEN003694-004
Protocol Title:	A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer
Version/Date:	Amendment 6 / 26 May 2022

APPROVALS:

The above study protocol or amendment has been reviewed and approved by below responsible person from Sponsor:

Print Name:	Signature:	Date:
[redacted]		