Zenith Epigenetics Ltd.

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

ZEN003694-004

1 ABBREVIATED CLINICAL STUDY REPORT

IND Number:	USA: 141108 China (for Expansion phase only): JXHL2000118, JXHL2000119
EudraCT Number:	2018-003906-26
Name of Investigational Product:	ZEN003694
Phase of Development:	2
Date of First Observation:	19 June 2019
Date of Last Observation:	24 July 2023
Study Termination Date:	12 July 2023
Indication Studied:	Triple-negative Breast Cancer
Study Design:	An open-label, non-randomized, dose escalation of ZEN003694 in combination with talazoparib in patients with triple-negative breast cancer
Sponsor's Contact:	[redacted]
Date of Report:	15 March 2024

This study was conducted in accordance with the International Council for Harmonisation tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents.

SIGNATURE PAGE

The signature page of the Sponsor's Responsible Medical Officer and/or Principal Investigator is provided in Appendix 16.1.5.

2 SYNOPSIS

<table>
<tr><td colspan="2">NAME OF COMPANY:
Zenith Epigenetics Ltd.</td><td>INDIVIDUAL STUDY SYNOPSIS</td></tr>
<tr><td>NAME OF FINISHED PRODUCT:
ZEN003694 + talazoparib</td><td>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</td><td>(FOR NATIONAL AUTHORITY USE ONLY)</td></tr>
<tr><td>NAME OF ACTIVE INGREDIENT(S):
ZEN003694</td><td>Volume:
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<tr><td colspan="3">Title of Study: A Phase 2 Study of ZEN003694 in Combination with Talazoparib in Patients with Triple-Negative Breast Cancer (ZEN003694-004)</td></tr>
<tr><td colspan="3">Investigators: The names and addresses of the investigators and their affiliations are available upon request.</td></tr>
<tr><td colspan="3">Study Sites: A total of 12 sites in the United States, Belgium, and Spain</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td colspan="2">Studied Period: 19 Jun 2019 to 24 Jul 2023</td><td>Phase of Development: 2</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary Objectives</u>
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 had received tumor-associated calcium signal transducer 2 (TROP2)-antibody drug conjugate (ADC) in the unresectable locally advanced or metastatic disease setting.
<u>Secondary Objectives</u>
Part 1
• To determine the pharmacokinetics (PK) of ZEN003694, its metabolite (ZEN003791), and talazoparib.
• To evaluate the effects of ZEN003694 and talazoparib on messenger RNA expression of pharmacodynamic (PD) 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 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.</td></tr>
</table>

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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 had 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 had received prior TROP2-ADC.
- To further evaluate the safety and tolerability of ZEN003694 in combination with talazoparib.
- To determine the 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.

Exploratory Objectives

Parts 1 and 2, Expansion

- [redacted]

Investigational Plan:

Part 1: Dose Escalation

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

Dose escalation was continued after all patients enrolled within a cohort had completed the 28-day Cycle 1 dose-limiting toxicity (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 were made based on clinical safety and (when available) PK data (maximum or peak concentration and area under the curve) after review by the Investigators and the Zenith Medical Monitor. If a DLT was observed in 1 of 3 patients in a cohort, 3 additional patients were enrolled into that cohort. If 1 of 6 patients in a cohort experienced a DLT, then dose escalation was continued in the next cohort or the MTD of the combination was declared. If ≥2 of 3 to 6 patients experience DLTs within a cohort, then the MTD was considered to have been exceeded and further dose escalation was ceased. In this case, if fewer than 6 patients had been enrolled at the previous dose level, that cohort was expanded to 6 patients to confirm the MTD. Should the MTD of the combination exceeded at Dose Level 1, a cohort was to be explored with a reduced dose of ZEN003694 or talazoparib. The MTD was defined as the highest dose level of ZEN003694 in combination with talazoparib at which no more than 1 of 6 patients experienced a DLT during the first cycle of therapy.

Enrollment in Part 1 of the study commenced with a 48 mg oral once daily (QD) dose as the starting dose for ZEN003694 in combination with a 1 mg oral QD dose of talazoparib. The dose of ZEN003694 was held constant throughout Cycle 1, however doses were held for the management of toxicity. The dose of talazoparib might have been held and reduced from the initial 1.0 mg dose in 0.25 mg increments in accordance with the talazoparib label

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and by agreement with Zenith. Alternative dosing schedules might have been evaluated based on the evaluation of clinical safety and upon agreement of the Investigators and Zenith.

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

Recommended Phase 2 Dose

The RP2D as determined in Part 1 of the study was defined as the dose level of ZEN003694 in combination with talazoparib recommended for further clinical study. The RP2D could 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 Design

Stage 1:

Once an RP2D of ZEN003694 in combination with talazoparib had been determined in Part 1, 17 patients were to be enrolled in Stage 1 of a Simon 2-stage design for evaluation of objective response (CR, partial response, or stable disease for ≥4 cycles) by Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). If there were ≥4 objective responses the study was to proceed to Stage 2. If there were <4 responses, the study was to be stopped.

Stage 2:

If at least 4 patients in Stage 1 had an objective response (complete response, partial response, or stable disease for ≥4 cycles) by RECIST 1.1, 20 patients were to be enrolled in Stage 2 of the Simon 2-stage design. Patients were to receive daily RP2D doses of ZEN003694 in combination with 1 mg talazoparib. Patients could 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 Cohorts

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

Expansion Cohort A: Combination Treatment in post-TROP2-ADC patients: 80 patients were to receive daily RP2D doses of ZEN003694 (48 mg QD) in combination with talazoparib (0.75 mg QD). Patients could continue

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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 Food and Drug Administration to assess any potential single-agent ZEN003694 activity, 10 patients were to initially receive daily doses of 48 mg ZEN003694 as monotherapy with the option to cross-over to combination treatment of 48 mg ZEN003694 plus 0.75 mg talazoparib at the time of disease progression (but no sooner than after 6 weeks of monotherapy). Patients in the cross-over group could 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 Patients:

Planned number of patients: Part 1 (Dose Escalation) and Part 2 (Stage 1 and 2): 52 patients; Expansion cohorts: 120 patients.

Actual number of patients: Part 1 (Dose Escalation) and Part 2 (Stage 1 and 2): 59 patients; Expansion cohorts: 24 patients.

Completed the study: None of the patients in Part 1 + Part 2 and Expansion cohorts completed the study. The reasons for study discontinuation were radiographic progression, clinical progression, death, other, adverse events (AEs), withdrawal by physician, withdrawal by patient, and termination of study by Sponsor.

Analyzed: All 83 enrolled patients (59 patients in Part 1 and Part 2, and 24 patients in Expansion cohorts) were included in the Safety Population.

Diagnosis and Criteria for Inclusion: Please see the clinical study protocol, Section 6 (Appendix 16.1.1) for the inclusion/exclusion criteria.

Test Product, Dose, Mode of Administration, and Batch Number(s):

The investigational product, ZEN003694 was ingested with a full (8-ounce) glass of water at least 1 hour before eating or 2 hours after eating. Each capsule was swallowed whole. Patients were advised not to chew, dissolve, or open the capsules. In Part 1 (dose escalation), the RP2D of ZEN003694 was established as 48 mg QD. In Part 2 and the Expansion phase, ZEN003694 was self-administered as 48 mg QD.

Talazoparib was administered as a 1 mg QD dose (as a starting dose in dose escalation, Part 1) and was taken at the same time as ZEN003694, at approximately the same time each day. In Part 2 and the Expansion phase, talazoparib was administered at a starting dose of 0.75 mg QD. As with ZEN003694, talazoparib was self-administered at least 1 hour before eating or 2 hours after eating (fasting). Talazoparib capsule was swallowed whole with a glass of water without chewing, dissolving, or opening them.

Batch or lot number(s):

ZEN003694 12 mg capsules: 170044 and 220029

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ZEN003694 48 mg capsules: 190012, 190113, and 220098 Talazoparib 0.25 mg: 19-002181, 20-UU-00010, and 18-001965 Talazoparib 1.0 mg: 18-000628		
[redacted]		
Reference Therapy, Dose, Mode of Administration, and Batch Number(s): Not applicable.		

Criteria for Evaluation:

Safety:

Demographic and Baseline Characteristics

Demographic and baseline characteristics were summarized for the Safety Population.

Demographic variables included age, sex, ethnicity, and race. Age was calculated in years relative to the informed consent date. Baseline characteristics included height (cm), weight (kg), body mass index (BMI) (kg/m^2), and Eastern Cooperative Oncology Group (ECOG) performance status.

Descriptive statistics were presented for age, height, weight, and BMI. Frequency counts and percentages were presented for sex, ethnicity, race, medical history, and ECOG performance status.

Adverse Event

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

In this study, all AE summaries were restricted to treatment-emergent adverse events (TEAEs), which were defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. In this study, only events that started after administration of study drug until 30 days after the last dose of study drug were considered AEs and recorded. Those that started before study drug administration were recorded on the Medical History case report form. If it was not determined whether the AE was treatment-emergent due to a partial onset date, then it was counted as treatment-emergent. Verbatim terms on CRFs were mapped to preferred terms (PTs) and system organ classes (SOCs) using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0.

Each AE summary was displayed by treatment group. Summaries that were displayed by SOC and PTs were ordered by descending order of patient incidence of SOC and PT within each SOC. Summaries of the following types were presented:

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Overall summary of TEAEs which contain an overview of each item below.

- Patient incidence of TEAEs and total number of unique TEAEs by MedDRA SOC and PT.
- Patient incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of patient summarization, a patient was classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity were noted as severity not reported for this summary.
- Patient incidence of TEAEs by MedDRA SOC, PT, and relationship (Related/Not Related) to ZEN003694, talazoparib, and either study drug. Related AEs were those reported as "Related" and unrelated AEs were those reported as "Not Related." At each level of patient summarization, a patient was classified according to the relationship if the patient reported 1 or more events. AEs with a missing relationship were noted as relationship not reported for this summary.
- Patient incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA SOC and PT.
- Patient incidence of serious TEAEs by MedDRA SOC, PT, and highest severity. At each level of patient summarization, a patient was classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity were considered life-threatening for this summary.
- Patient incidence of serious TEAEs by MedDRA SOC, PT, and relationship (Related/Not Related) to ZEN003694, talazoparib, and either study drug. Related AEs were those reported as "Related" and unrelated AEs were those reported as "Not Related." At each level of patient summarization, a patient was classified according to the relationship if the patient reported 1 or more events. AEs with a missing relationship were noted as relationship not reported for this summary.
- Patient incidence of TEAEs leading to death as an outcome by MedDRA SOC and PT.
- Patient incidence of TEAEs leading to study discontinuation by MedDRA SOC and PT.

Serious adverse event

A serious adverse event was any AE that resulted in death, was life-threatening, required in-patient hospitalization or prolonged existing hospitalization, resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, resulted in a congenital anomaly or birth defect, or was any other important medical event.

Study Endpoints: For study endpoints, see Section 12 of the Protocol Amendment 6.0 (Appendix 16.1.1).

Statistical Methods: The planned statistical analysis methods are described in detail in the statistical analysis plan (SAP). The latest SAP, dated 01 September 2023, is provided in Appendix 16.1.9.

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SUMMARY OF RESULTS

Efficacy Results: [redacted]

Safety Results:

Part 1 (Dose Escalation) and Part 2 (Stage 1 and 2)

- All 59 (100.0%) treated patients experienced a TEAE in Part 1 and Part 2 of the study, of whom 58 patients (98.3%) experienced TEAEs related to ZEN003694, talazoparib, and ZEN003694 or talazoparib. The majority of TEAEs were Grade 3 (29 patients, 49.2%) or Grade 2 (18 patients, 30.5%) in severity.
- The most commonly reported TEAEs (≥10 patients) by PT were nausea (28 patients, 47.5%); platelet count decreased (24 patients, 40.7%); fatigue (22 patients, 37.3%); vomiting and decreased appetite (18 patients each, 30.5%); aspartate aminotransferase increased and thrombocytopenia (16 patients each, 27.1%); alanine aminotransferase increased, dysgeusia, anaemia, and dyspnoea (13 patients each, 22.0%); photopsia (12 patients, 20.3%); and constipation and hypertension (11 patients each, 18.6%).
- A total of 28 serious TEAEs were observed in 17 patients (28.8%). Serious TEAEs reported for ≥2 patients were dyspnoea and thrombocytopenia (3 patients each; 5.1%) and pleural effusion (2 patients, 3.4%).
- A total of 6 (10.2%) patients experienced TEAEs leading to study discontinuation: diarrhoea, nausea, thrombocytopenia, and dyspnoea (in 1 patient), pulmonary embolism, gait disturbance, and platelet count decreased.
- Four patients (6.8%) had TEAEs leading to death, 3 patients in the Part 2 ZEN 48 mg + talazoparib (TAL) 0.75 mg treatment group (due to status epilepticus, disease progression, and pulmonary embolism) and 1 patient in the Part 1 ZEN 48 mg + TAL 1 mg treatment group (due to haemorrhage intracranial). The 4 TEAEs leading to death were not related to either ZEN003694 or talazoparib.
- Three DLTs were observed in the Part 1 ZEN 48 mg + TAL 1 mg cohort (fatigue and 2 events of platelet count decreased), while 1 DLT was observed in the Part 1 ZEN 48 mg + TAL 0.75 mg cohort (platelet count decreased).

Expansion Cohorts

- All 24 treated patients (100.0%) experienced a TEAE, of whom 22 patients (91.7%) each reported at least 1 TEAE related to ZEN003694 and ZEN003694 or talazoparib, while 19 patients (79.2%) reported at least 1 TEAE related to talazoparib.
- The most commonly reported TEAEs (≥5 patients in total) by PT were fatigue (13 patients, 54.2%); nausea and platelet count decreased (11 patients each, 45.8%); anaemia (10 patients, 41.7%);

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hyperglycaemia (8 patients, 33.3%); decreased appetite (7 patients, 29.2%); and dyspnoea (6 patients, 25.0%); vomiting, constipation, aspartate aminotransferase increased, vision blurred, hyponatraemia, dysgeusia, and back pain (5 patients each, 20.8%).

- A total of 25 serious TEAEs were observed in 10 patients (41.7%). Serious TEAEs reported for ≥2 patients were dyspnoea (3 patients, 12.5%), pleural effusion, and muscular weakness (2 patients each, 8.3%).
- One patient (4.2%) in Cohort A experienced a TEAE leading to both study discontinuation and death: pericardial effusion. The TEAE of pericardial effusion was not related to either ZEN003694 or talazoparib, but the cause of death was considered to be related to the underlying disease.
- The majority of TEAEs were Grade 2 in severity (10 patients, 41.7%), followed by Grade 3 (9 patients, 37.5%). The majority of serious TEAEs were Grade 3 in severity (6 patients, 25.0%), followed by Grade 4 (2 patients, 8.3%).
- A total of 17 DLTs were observed in 3 patients in Cohort A: 5 events of platelet count decreased, 3 events of dyspnoea, 2 events of vomiting, and 1 event each of decreased appetite, dysgeusia, nausea, weight decreased, atelectasis, hyperglycaemia, and hypoxia.

Conclusions: Although this was an early terminated study, ZEN003694 in combination with talazoparib demonstrated a manageable safety profile in patients with locally advanced or metastatic TNBC.

Date of Report: 15-Mar-2024