Æterna Zentaris

Clinical Trial Protocol

Clinical Trial No.	**AEZS-108-050**
Clinical Phase	**III**
Type of Study	**Therapeutic confirmatory**
Title	**Randomized controlled study comparing AEZS-108 with doxorubicin as second line therapy for locally advanced, recurrent or metastatic endometrial cancer**
Design	**Open-label, randomized, active-controlled, multicenter trial**
Versions	**No. 3.2: 12 September 2014** No. 3.1: 12 March 2014 No. 3.0: 20 November 2013 No. 2.0: 11 July 2013 No. 1.2.1: 29 April 2013 No. 1.2: 13 March 2013 No. 1.1: 19 December 2012
EudraCT No.	**2012-005546-38**

Sponsor **Aeterna Zentaris GmbH**
Weismüllerstraße 50
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Germany

PROTOCOL AUTHORIZATION

Titlc: Ran<lomizcd controllcd study compa1fog AEZS-108 with doxorubid n as second line thcrapy for locally advanccd, rccurrcnt or mctastatic cndomctria) cancer
Opcn-labcl, randomizcd, activc-controlJed, multicenter trial

Study nmn bcr: A EZS-108-050
Version No./ Date: Version 3.2 / 12 September 2014

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Date. Signaturc 25 Sep 2014

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Protocol Authorization by Country-specific Coordinating Investigator

Country **Coordinating investigator**

_____
Date, Signature

Investigator Agreement

I have read the protocol and understand the requirements of this clinical trial. I agree to conduct the study in compliance with this protocol.

_____
Name of Investigator (Print Name)

_____ _____
Signature of Investigator Date (DD/MMM/YYYY)

Study site: _____

_____

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Telephone number: _____

Fax number: _____

Protocol Authorization and Investigator Agreement

Investigator Agreement

I have read the protocol and understand the requirements of this clinical trial. I agree to conduct the study in compliance with this protocol. I will forward the protocol to my Ethics Committee / Institutional Review Board for approval.

_____
Name of Investigator (Print Name)

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Signature of Investigator Date (DD/MMM/YYYY)

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For further country-specific contacts, please refer to the current list in the Study Manual.

Notification of serious adverse events

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Central laboratory

Analysis of tissue specimens for LHRH receptor expression

An assay for LHRH receptor expression is currently under development and expected to become available and applied while this study is ongoing. Therefore, archival formalin-fixed and paraffin-embedded (FFPE) specimens (blocks) must be retained at the site. Similarly, FFPE blocks must be prepared from any fresh biopsy material obtained during screening. Study sites will be instructed about the timing and specific conditions of the specimens to be submitted.

Assay of AEZS-108, doxorubicin and doxorubicinol:

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Core lab for central evalation of ECGs (PK sub-study only):

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LIST OF ABBREVIATIONS AND TERMS

ADR	adverse drug reaction
AE	adverse event
AEZS	Aeterna Zentaris
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie (Gynecological cancer study group)
ALAT	alanine amino transferase (= serum glutamate pyruvate transaminase, SGPT)
ANC	absolute neutrophil count
ANOVA	analysis of variance
AP	alkaline phosphatase
App	appendix
ASAT	aspartate amino transferase (= serum glutamate oxalo-acetate transaminase, SGOT)
ATC	anatomic, therapeutic, chemical (classification system for drugs)
AUC	area under the curve
BP	blood pressure BSA
	body surface area BW
	body weight
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (NCI)
DOX	doxorubicin
DLT	dose limiting toxicity
DRL	Drug Reference List (WHO coding thesaurus)
DSMB	Data and Safety Monitoring Board
ECHO	echocardiography
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	ejection fraction
EOI	end of infusion
ESR	erythrocyte sedimentation rate
FFPE	formalin-fixed and paraffin-embedded
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FSH	follicle stimulating hormone
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GnRH	gonadotropin releasing hormone
γ-GT	gamma-glutamyltransferase
HCG	human chorion gonadotropin

HR	heart rate (as measured by ECG)
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Independent Review Board
ITT	intention-to-treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web-based randomization stem
LDH	lactate dehydrogenase
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone (synonym: GnRH)
LKP	Leiter der Klinischen Prüfung (Study Director according to § 40 German Drug Law)
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MDR	multi-drug resistance
MRI	magnetic resonance imaging
MUGA	multigated radionuclide angiography
NCI	National Cancer Institute (U.S.)
ORR	overall response rate
OS	overall survival
PLD	pegylated liposomal doxorubicin
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
PP	per-protocol
PR	partial response
PT	preferred term (MedDRA)
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RNV	radionuclide ventriculography
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System (tradename)
SD	stable disease
SOC	system organ class (MedDRA)
$t_{1/2}$	elimination half-life time
TEAE	treatment emergent adverse events
TMF	trial master file
TTP	time to progression
ULN	upper limit of normal range
WBC	white blood cell
WHO	World Health Organization

SYNOPSIS

Study No.	AEZS-108-050	**Clinical phase**	III
EudraCT No.	2012-005546-38	**Type of study**	Therapeutic confirmatory
Clinical-Trials.gov	NCT01767155	**Indication**	Endometrial cancer, advanced, recurrent or metastatic

Title of the study

Randomized controlled study comparing AEZS-108 with doxorubicin as second line therapy for locally advanced, recurrent or metastatic endometrial cancer

Coordinating investigator(s)

Global and North American sites:

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European sites:

Hani Gabra
Imperial College London Hammersmith Campus
London, UK

Study centers:

Approximately 120 study locations (CAN/Europe/Israel/USA).

Study period planned

3 years; Q1.2013 – 12.2015

Objectives

Primary: Compare the overall survival (OS) of patients treated with AEZS-108 to the OS of patients treated with doxorubicin.

Secondary: Compare efficacy based on progression-free survival (PFS), overall response rate (ORR), and clinical benefit rate (CBR).
Subgroup analyses of efficacy parameters in relation to tumor LHRH receptor expression.

Compare safety.

Determine the impact of these regimens on patient-reported quality of life.

Sub-study (selected study sites only):
Assess pharmacokinetics of AEZS-108, doxorubicin, and doxorubicinol.
Assess acute effects of AEZS-108 and doxorubicin on electrocardiographic parameters.

Methodology / Design

Open-label, randomized, active-controlled, two-arm Phase III study to compare the efficacy and safety of AEZS-108 and doxorubicin. The study will include about 500 patients with advanced, recurrent or metastatic endometrial cancer who have

progressed and who have received one chemotherapeutic (i.e., cytotoxic) regimen with platinum **and** taxane (either as adjuvant or first line treatment).

Patients will be centrally randomized in a 1:1 ratio to receive treatment with either AEZS-108 (Arm A) or doxorubicin (Arm B).

During ongoing treatment, response will be evaluated every 3 cycles; earlier reassessments should be scheduled to verify a response (no earlier than 4 weeks after first observation of the response) or in case of suspected progression. Patients, who have gone off-treatment for reasons other than progression, will be reassessed every 12 weeks until progression. All patients will be followed-up for survival.

On a regular basis, at intervals no longer than 6 months, results from safety analyses will be submitted to an independent Data and Safety Monitoring Board (DSMB) that will advise the Sponsor of potentially critical findings.

The final analysis will be performed after about 384 deaths have been observed. There will be two planned interim analyses; the first will be for futility only, the second will be for safety and efficacy.

Based on the availability of the assay for LHRH receptor expression in tumor specimens, subgroup analyses stratified for extent of LHRH receptor expression will assess the predictive value of the LHRH receptor assay.

A sub-study, at selected sites, will investigate the pharmacokinetics of AEZS-108, doxorubicin and doxorubicinol and assess the acute effects on electrocardiographic parameters.

Sparse PK sampling will be performed, at all sites where feasible, to explore exposure-response relationships between AEZS-108 and its metabolites and measures of safety and efficacy.

Number of patients planned

Approximately 500 (250 per treatment arm).

Inclusion criteria

1. Women ≥ 18 years of age
2. Histologically confirmed endometrial adenocarcinoma of any subtype.
    a. Endometrioid carcinoma
        i. Variant with squamous differentiations
        ii. Villoglandular variant
        iii. Secretory variant
        iv. Ciliated cell variant
    b. Mucinous adenocarcinoma
    c. Serous adenocarcinoma
    d. Clear cell adenocarcinoma
    e. Mixed cell adenocarcinoma
    f. Squamous cell carcinoma
    g. Transitional cell carcinoma
    h. Small cell carcinoma
    i. Undifferentiated carcinoma

3. Advanced (FIGO stage III or IV), recurrent or metastatic disease.
4. Measurable or non-measurable disease that has progressed since last treatment.
5. Patients with advanced, recurrent, or metastatic endometrial cancer who have received one chemotherapeutic regimen with platinum **and** taxane (either as adjuvant or as first line treatment) and who have progressed.
6. Availability of fresh or archival FFPE tumor specimens for analysis of LHRH receptor expression.

Exclusion criteria

Safety concerns:

1. ECOG performance status > 2.
2. Inadequate hematologic, hepatic or renal function
   - thrombocyte count:< 100 x 10^9/L;
   - absolute neutrophil count (ANC):< 1.5x 10^9/L;
   - hemoglobin:< 5.6 mmol/L (< 9 g/dL);
   - ASAT, ALAT, AP:> 2.5 times upper limit of normal range (ULN) (> 5x ULN if clearly related to liver metastases);
   - creatinine, bilirubin:> 1.5x ULN.
3. Red blood cell transfusion within 2 weeks prior to anticipated start of study treatment.
4. History of myocardial infarction, acute inflammatory heart disease, unstable angina, or uncontrolled arrhythmia within the past 6 months.
5. Impaired cardiac function defined as left ventricular ejection fraction (LVEF) < 50 % (or below the study site's lower limit of normal) as measured by MUGA or ECHO.
6. Concomitant use of prohibited therapy (as specified in Section 6.3.2).
7. Chemo-, immune-, or hormone-therapy within 5 elimination half-life times or 4 weeks prior to randomization, whichever is the shorter. Radiotherapy (including pre- or post-operative brachytherapy) within 4 weeks prior to randomization.
8. Previous anthracycline-based chemotherapy (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone and valrubicin), in any formulation.
9. Anticipated ongoing concomitant anticancer therapy during the study.
10. History of serious co-morbidity or uncontrolled illness that would preclude study therapy, such as active tuberculosis or any other active infection.
11. Brain metastasis, leptomeningeal disease.
12. Pregnant or lactating female or female of childbearing potential not employing adequate contraception. Women of childbearing potential must agree to employ adequate contraception until 6 months after the last dose of study drug, defined as
    - complete abstinence; (Note: acceptable only as "true abstinence", i.e. when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence, (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
    - any intrauterine device (IUD) with published data showing that the lowest expected failure rate is < 1 % per year; or
    - any other methods with published data showing that the lowest expected failure rate is less than 1 % per year.
13. Subjects with known hypersensitivity to peptide drugs, including LHRH agonists.

Lack of suitability for the trial:

22. Malignancies arising from the uterine cervix.
23. Uterine sarcomas or mixed epithelial and mesenchymal tumors including carcinosarcoma, adenosarcoma, or carcinofibroma.
14. Receipt of 2 or more prior cytotoxic chemotherapy regimens for advanced, recurrent, or metastatic endometrial cancer.
15. Prior treatment with AEZS-108.
16. Use of LHRH agonist or antagonist treatment within 6 months prior to randomization *(see* Appendix 5 *for examples of drug names)*.
17. Malignancy within last 5 years except non-melanoma skin cancer.
18. Any concomitant disease or condition that would interfere with the subjects' proper completion of the protocol assignment.
19. Concomitant or recent treatment with other investigational drug (within 4 weeks or 5 elimination half-life times prior to anticipated start of study treatment).

Administrative reasons:

20. Lack of ability or willingness to give informed consent.
21. Anticipated non-availability for study visits/procedures.

Study medication, dose, and mode of administration

AEZS-108	INN zoptarelin doxorubicin, acetate salt
Presentation:	100 mg lyophylisate per vial
Dosage scheme:	267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles Note: If the body weight is +/- 10% of the body weight measured at day 1 of the preceding cycle, the body weight measured at day 1 of the preceding cycle may be used for calculating the dose to be prepared in the pharmacy
Maximum duration / dose:	The proposed maximum duration is 9 cycles.
Treatment delay:	up to 2 weeks in case of persisting clinically significant adverse reactions (except for alopecia); for details, see Protocol Section 6.3.1.3.
Dose reduction:	210 mg/m^2 in case of dose-limiting toxicity or delayed recovery
Doxorubicin	doxorubicin HCl *(non-liposomal formulation)*
Presentation:	commercial product (trade name, e.g., Adriamycin)
Dosage scheme:	60 mg/m^2 by intravenous bolus injection, 1-hour intravenous infusion, or according to standard institution procedures, on Day 1 of 21-day (3-week) cycles Note: If the body weight is +/- 10% of the body weight measured at day 1 of the preceding cycle, the body weight measured at day 1 of the preceding cycle may be used for calculating the dose to be prepared in the pharmacy
Dose adjustment:	(for starting dose)
- Renal function	at glomerular filtration rate (GFR) below 10 ml/min.: 75 % of calculated dose
- Hepatic function	at serum bilirubin 1.2 to 3.0 mg/100 mL: 50 % of calculated dose;

	at serum bilirubin > 3.0 mg/100 mL: 25 % of calculated dose
Maximum duration / dose:	up to a cumulative lifetime dose of 550 mg/m^2
Treatment delay:	up to 2 weeks in case of persisting clinically significant adverse reactions (except for alopecia); for details, see Protocol Section 6.3.2.3.
Dose reduction:	(for retreatment) 50 to 75 % of starting dose if required by dose-limiting toxicity or delayed recovery

Criteria for evaluation (efficacy, safety)

1. Overall survival (primary efficacy endpoint).

2a Efficacy: Progression-free survival (PFS), overall response rate (ORR = CR + PR) and clinical benefit rate (CBR) will be evaluated as CR + PR + SD for at least 3 months.

2b. Safety: adverse events, clinical laboratory, ECG and LVEF.

2c. Quality of Life: EORTC QLQ30 + QLQ-EN24 questionnaires.

2d. Pharmacokinetics (PK sub-study) and exposure-response relationship.

Statistical methods

The primary efficacy variable will be overall survival (OS). The primary analysis of the primary efficacy variable will be based on the ITT population. The final OS analysis, which is event-based, will be conducted after approximately 384 randomized patients have died. In the primary analysis, a log-rank test with an overall two-sided Type I error rate of 0.05 after taking the interim analyses into account will be used to compare OS between the two treatment arms via a SAS lifetest procedure. Kaplan-Meier estimates will be used to calculate median OS and the 95% confidence interval of the median OS. The proportion of patients alive at six and 12 months (from randomization date) and the 95% confidence intervals for these estimated proportions, if appropriate, will be presented.

Approximately 384 events of deaths will be required to achieve 80 % power to detect a treatment difference at the two-sided 0.05 significance level. It is expected that approximately 500 patients will be enrolled during an estimated 24-month recruitment period and will then be followed for 12 months to observe a total of approximately 384 death events. In the sample size calculation, it is assumed that the median OS is 12 months for AEZS-108 and 9 months for doxorubicin. The sample size calculation has taken two planned interim looks into account, the first being a futility analysis only.

Population pharmacokinetic methodology will be applied to analyze results derived from sparse PK sampling and from the PK sub-study.

FLOW CHART

Procedures	**Screen**	**Cycle 1**		**Cycle 2 to 9**	**End of therapy**	**Post Therapy Follow up**
Visit / Cycle Day **1)**	**Within 4 wks before C1 D1 2)**	**D1**	**D8 + D15 (+D22 + D29** if retreatment delayed**) 3)**	**4)**	**3-5 weeks after last dose 5)**	**Every 3 months 6)**
Informed consent	**X**					
Demographics	**X**					
Medical history	**X**					
Physical examination	**X**					
Interval history and symptom-directed exams		**X**		**D1**	**X**	
Clinical assessments: Height (screen only), Weight ECOG performance status Blood pressure, pulse	**X** **X** **X**	**X** **X** **X**	 **X**	**D1** **D1** **D1**	**X** **X** **X**	 **X** *(until PD)* **X** *(until PD)*
Adverse events		**Cumulative recording** [7] *(whenever observed/applicable)*				**X**[9]
Concomitant treatments	**X**	**X**		**D1**	**X**	**X**[10]
Clinical laboratory tests Hematology, Chemistries, and Urinalysis LH, FSH Pregnancy test (ß-HCG)	**X** **X** **X** [8]	**X**	**X**[11]	**D1** [4] **D1**	**X** **X**	
Tumor tissue collection	**X** [14]					
Pharmacokinetics: - Sparse PK sampling [17] - PK sub-study [12]		**X** **(X)**	**(D2-D4)**	**Cycle X D1**[12] **(once, if not done at C1)**		
Cardiac function test LVEF (ECHO or MUGA) ECG (12-lead)	**X** [2A] **X**	 **X**[12]	 **D2**[12]	**End of C3, C6, C7, C8**[16] **D1**	**X** **X**	**X** [9] **X** [9]
Tumor imaging/evaluation	**X** [2B]			**End of C3 + C6**	**X**	**X**
Quality of Life questionnaire	**X**			**End of C3 + C6**	**X**	**X**
Survival follow-up						**X**
Patient registration	**X**					
Eligibility criteria review	**X**	**X**[15]				
Randomization[13]	**D-1 to D-4**[13]					

Study treatment		**X**		**D1**		

1) A window of +/- 3 days will be allowed for scheduled visits/actions, +/- 7 days for 3 monthly follow-ups. If a procedure or visit falls on a public holiday, the patient should be scheduled for the next working day.
2) Pre-study evaluations dating back more than 2 weeks prior to treatment start are acceptable.
   2A) LVEF: In absence of intercurrent chemotherapy or cardiac medical history, results dating back up to 8 weeks will be acceptable.
   2B) Tumor imaging: Assessments of indicator lesions up to 4 weeks prior to treatment start (C1D1) will be considered valid for baseline evaluation.
3) Patients who have not recovered sufficiently from treatment-related adverse events within 3 weeks may have their retreatment delayed by up to 2 weeks; patients who cannot be retreated 5 weeks after previous dose, will not receive further study treatment but will still be followed for outcome.
4) Start of a new cycle is planned every 3 weeks unless treatment delay is required due to residual toxicity. Per footnote 1, a window of up to 3 days is allowed to schedule tests prior to the anticipated day of retreatment, to assure sufficient recovery from treatment-related adverse events ('toxicity') prior to dosing.
5) A full End-of-Therapy assessment will be also required whenever a patient is being withdrawn from the study. The reason(s) for discontinuation will be documented.
6) Patients discontinuing study treatment for reasons other than disease progression will be reassessed at 3-month intervals to assess the time to treatment failure (progression / death).
   Follow-up until progression will be suspended in patients in whom a new cancer treatment has been started without prior documentation of progressive disease.
   Information on survival status may be captured by telephone if no follow-up visit is scheduled for other reasons.
7) If treatment was discontinued because of a drug-related adverse event (i.e., causality at least possibly related), the patient will be followed up as clinically indicated to assess and document the outcome.
8) Only required in women of child-bearing potential
9) Only a patient developing signs of cardiac failure during post-treatment follow-up will have LVEF and ECG evaluated; a left ventricular dysfunction of CTCAE grade 4 will be reported as an SAE.
10) Only anticancer treatments that a patient received during post treatment follow-up for survival will be recorded.
11) For tests performed by a laboratory not affiliated to study site (e.g. mid-cycle controls by the patient's home doctor) copies of the external laboratory reports will be provided to the sponsor and results recorded in the CRF.
12) A PK sub-study, including electrocardiographic evaluations on Day 1 and Day 2, will be conducted at selected investigational sites. Procedures are described in APPENDIX 7
13) Every effort should be made to start treatment within 4 days of randomization.
14) Specimens from FFPE fresh biopsies if FFPE archival tumor specimens are not available.
15) Except for Day 1 clinical laboratory tests
16) Recommended to be conducted also at end of Cycle 7 and 8 (i.e., before start of Cycle 8 and Cycle 9, respectively) for both arms. Results are to be captured on the eCRF if there is an abnormal finding.
17) Sparse PK sampling of AEZS-108 treated patients will be performed at all investigational sites, where feasible. Sparse PK sampling is expected in Cycle 1 or alternatively in a subsequent cycle of ongoing patients, within the following time windows:
   sample #1: within 60 minutes before end of the 2-hour infusion (during 2nd half of the infusion period);
   sample #2: between 30 and 60 minutes after the end of infusion (EOI);
   sample #3: between 120 and 180 minutes after EOI;
   sample #4 (optional): between 4 and 6 hours after EOI.

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1 BACKGROUND INFORMATION AND RATIONALE

1.1 Background information on LHRH receptors and endometrial cancer

LHRH receptor expression in gynecological cancers

LHRH, also known as GnRH, is a hormonal decapeptide produced by the hypothalamus, which plays a pivotal role in the regulation of the pituitary/gonadal axis, and thus, in the production of sex steroids. Because sex steroids have been implicated in the development of breast and other gynecological cancers, the role of LHRH and its receptor in these tumors has been studied. While breast cancers were found positive for LHRH receptors in up to 50 % of cases, more than 80 % of ovarian and endometrial cancers have been reported to have functional binding sites for LHRH [17, 21, 22], which are targeted by AEZS-108 (see Section 1.2.1 below).

Endometrial cancer

Cancer of the endometrium is the most common gynecologic malignancy and accounts for 6 % of all cancers in women. The majority of the cases occur in postmenopausal women, with the largest number of women developing their cancers during the sixth decade.

The most common histological form of endometrial cancer cell type (about 80 % of all cancers) is endometrioid adenocarcinoma [18]. Serous, clear cell, mucinous, squamous, and undifferentiated tumors are rarely encountered. While in many cases primary therapy of endometrial cancer results in cure, in some 25 % of the patients recurrences are seen, commonly within 3 years after diagnosis. Recurrent tumors locally confined to the vagina may be cured in some cases with combined surgery and radiation therapy; systemic recurrences are usually considered incurable and are typically treated with systemic therapy.

Systemic drug therapy

Patients with advanced or recurrent tumors that are progesterone receptor-negative or do not response to hormonal therapy should be considered for chemotherapy.

Active agents include anthracyclines, platinum compounds, and taxanes. Observed single agent response rates vary between 20-35 %. Responses rates have increased when various combination therapies were employed although it remains unclear whether this confers any survival advantage [4, 15, 19].

Please refer to Section 1.3 for details on the selection of doxorubicin as comparator drug for this study.

1.2 Background information on AEZS-108

AEZS-108 (INN zoptarelin doxorubicin, formerly known as AN-152 or ZEN-008) is a LHRH-cytotoxic hybrid molecule. The cytotoxic molecule doxorubicin (DOX) is chemically linked to the carrier molecule D-Lys^{6}-LHRH (an LHRH agonist) which enables the specific binding and selective uptake of the hybrid molecule by tumors expressing receptors for LHRH (“drug targeting”).

In clinical Phase I and Phase II studies, AEZS-108 has been studied and shown therapeutic activity in patients with LHRH receptor-positive ovarian and endometrial cancer. Based on its pharmacological mode of action, AEZS-108 is expected to also be active in other LHRH receptor-positive cancers and studies are currently ongoing in patients with triple negative breast cancer, urothelial, and hormone-refractory prostatic cancer.

For more details on AEZS-108, please refer to the current Investigator's Brochure. See also Engel et al. [8] for an overview on the preclinical and clinical development of AEZS-108.

1.2.1 Nonclinical pharmacology and toxicology

Mechanistic in vitro studies showed that uptake of doxorubicin into LHRH-receptor expressing cells was facilitated by the presence of the LHRH analog moiety. In addition, AEZS-108 had a greater ability to enter the nucleus of living cells compared to dead (photodamaged) cells. The cytotoxicity of AEZS-108 was demonstrated in several LHRH receptor-positive cell lines derived from estrogen-dependent human breast cancer, estrogen-independent mouse mammary carcinoma, ovarian, endometrial, oral and laryngeal cancer [13]. In LHRH receptor-negative cell lines, AEZS-108 was not active or significantly less active than DOX.

In vivo xenograft tumor models in nude mice showed AEZS-108 to be effective in various tumor models for breast, ovarian, endometrial, and prostate. At equimolar doses, the efficacy of AEZS-108 was superior to that of doxorubicin and not accompanied by its substantial mortality.

In **pharmacokinetic** studies in rats and dogs, $t_{1/2}$ (< 1 hr) and t_{max} (0.08 hr) of AEZS-108 and DOX were similar. Dose linearity for AEZS-108 was demonstrated when based on C_{max} and $AUC_{0-4.}$ The AUCs of AEZS-108 were higher (3 to 9 times in rats, 7 to 12 times in dogs) than those of DOX after single and multiple doses, independent of dose and sex.

AEZS-108 is sensitive to spontaneous and/or carboxylesterase-catalyzed deconjugation into DOX and probably D-Lys^6-LHRH-glutarate in blood plasma and aqueous solutions. The rate of hydrolysis of AEZS-108 in mouse serum (approx. $t_{1/2}$ = 20 min.) was significantly higher than in human serum (approx $t_{1/2}$ = 100 – 120 min.). AEZS-108 in microsomal liver incubations suggested a more secondary role of metabolic decomposition than spontaneous hydrolysis.

In **safety pharmacology** studies, AEZS-108 showed no influence on neuropharmacological parameters or on motor coordination when examined at doses up to 15 mg/kg given by intravenous administration. In dogs, when AEZS-108 was administered IV (4.8 mg/kg) over 1 hour, effects were noted as a decrease of the peripheral arterial blood pressure and as an increase of heart rate, cardiac output and respiratory rate and volume. No effects on cardiovascular, electrocardiographic, and respiratory parameters were observed at lower doses.

In acute **single dose toxicity** studies in mice and rats, AEZS-108 (20 – 80 mg/kg intra-venous (IV) single dose) induced qualitatively similar signs of toxicity to DOX (10 - 40 mg/kg single dose IV). The no-observed effect level (NOEL) and the LD_{50} of AEZS-108 and DOX were similar if compared on a molar basis.

In acute **single dose toxicity** studies in mice and rats, AEZS-108 induced qualitatively similar signs of toxicity to equimolar doses of doxorubicin. When compared at molar dosages, the NOAEL and the LD50 of AEZS-108 and doxorubicin were also similar. Most frequent signs of toxicity were reduced motility, ataxia, dyspnea, and reduced muscle tone. Histopathology findings following treatment with AEZS-108 involved seminal vesicles and ovaries, indicating that these may be target organs.

In **repeated-dose toxicity** studies in rats and dogs, AEZS-108 in doses of 0.3 to 15 mg/kg weekly for 4 weeks induced qualitatively similar signs of hematology toxicity to doxorubicin. In rats, histopathology findings, preferably following mid and high doses of AEZS-108, consisted of atrophy in the male and female genital tract, in the lymphatic system, and in the mucosa of the gastrointestinal tract. In dogs, slow infusion periods were required to avoid fairly pronounced signs of toxicity. Morphological changes were revealed in the male and female genital system with 1.2 to 4.8 mg/kg and in the lymphocytic system of animals treated with 4.8 mg/kg reflecting the cytostatic nature of AEZS-108. Most changes had subsided at the end of the 8-week recovery period. However, AEZS-108-related degeneration of the germinative epithelium of the Sertoli cells in the testes was still present.

No changes were noted for electrocardiography (only dogs) and histopathology of the heart in both species. The lowest lethal dose of AEZS-108 following weekly administration for 4 weeks was 15 mg/kg in rats and > 5 mg/kg in dogs. In both species, if compared on molar basis, the NOAEL and the lowest lethal dose of AEZS-108 and doxorubicin were similar.

Local tolerance. No signs of local intolerance were found in rats, rabbits, and dogs after IV and in rabbits after intraarterial injection.

1.2.2 Clinical data

Pharmacokinetics

Following administration of 160 and 267 mg/m^2 AEZS-108, maximum plasma concentrations of 728 – 6661 ng/ml were measured. Because of the high variability, neither a dose dependency of C_{max} values nor of the calculated AUC values could be shown. The calculated half-life and the clearance of AEZS-108 were found to be in the range of 0.74 - 4.58 h and 0.37 – 2.67 (l/min·m^2), respectively, and were independent of the dose level. This is an indication of dose linearity.

At the dose levels of 160 and 267 mg/m^2, the C_{max} values of the active metabolite doxorubicin were measured in the range of 177 – 1580 ng/ml. The half-life and calculated clearance for doxorubicin were found to be in ranges comparable to those for AEZS-108. The doxorubicin plasma concentrations and therefore the calculated AUC values of doxorubicin increased with increasing dose.

Safety

The safety profile, described below is derived from the Investigator's Brochure (edition 5, May 23, 2012); it is based on 3 completed clinical studies in 102 female patients (Phase I:

17, Phase II: 42 patients with ovarian cancer, 43 patients with endometrial cancer) and 2 ongoing clinical studies in approximately 21 urothelial or prostate cancer patients.

The most frequent adverse drug reactions (ADRs) i.e., AEs considered as likely or possibly related to AEZS-108) were hematological (anemia, leukopenia, neutropenia), cutaneous (alopecia), general (fatigue, mucosal inflammation) and gastrointestinal (diarrhea, nausea, vomiting). Table 1 of the Investigator's Brochure provides an 'Overview on suspected adverse drug reactions (ADRs) to AEZS-108'.

Hematotoxicity was potentially dose limiting but was usually rapidly reversible and did not require deviation from scheduled retreatment or discontinuation of AEZS-108. In fewer than 10 % of the patients, retreatment was delayed due to hematotoxicity, by one to two weeks. Approximately 5 % of the patients received a blood transfusion, 15 % of the patients received G-CSF and three patients out of 102 (3 %) had a dose reduction to 160 mg/m2.

The most frequent serious adverse drug reactions were leukopenia, vomiting, and nausea.

In the Phase II **endometrial cancer** study [7], 28 patients out of 43 (65.1 %) completed 6 cycles of treatment. The most frequent AEs judged related to AEZS-108 were nausea (39.5 %), alopecia (37.2 %), fatigue (25.6 %), vomiting (20.9 %), anemia (16.3 %), and neutropenia (16.3 %). The most frequent grade 3 or 4 AEs judged related to AEZS-108 were neutropenia (11.6%) and leukopenia (9.3 %). No cardiac toxicity was reported based on LVEF.

Two patients out of 43 (4.7 %) died within 30 days of the last dose of AESZ-108: in one case, the patient died of malignant disease. The other death was due to acute respiratory distress syndrome and was judged unrelated to AEZS-108. SAEs (other than death) were observed in 13 patients out of 43 (30.2 %). In six patients out of 43 (14 %) the SAE was judged related to AEZS-108. They consisted of hemoglobin decreased, blood creatinine increased, ileus, pulmonary embolism, white blood cell count decreased and influenza-like illness. No AEs (other than deaths or SAEs) or abnormalities in laboratory parameters led to AEZS-108 discontinuation.

The most frequent grade ≥ 3 hematological abnormalities were leukopenia, neutropenia, and lymphocytopenia. Leukopenia of grade ≥ 3 was observed at each cycle (in 13 % to 26 % of the patients) and only on Day 15. Neutropenia of grade ≥ 3 was observed at each cycle (in 32 % to 54 % of the patients) and only on Day 15. Lymphocytopenia of grade ≥ 3 was observed at each cycle on day 8 (in 6 % to 20 % of the patients) and in some cases on Day 15 and 22. Hematotoxicities were easily manageable as none were reported as a serious AE and/or led to AEZS-108 discontinuation. Leukopenia delayed by ≥ 7 days AEZS-108 administration in approximately 5 % of the patients.

Efficacy

In Phase I and Phase II studies, AEZS-108 has shown therapeutic activity in patients with LHRH receptor-positive ovarian and endometrial cancer. In the Phase II study in 42 patients with advanced or recurrent ovarian cancer with LHRH positive tumors, AEZS-108 was shown to be active based upon an ORR of 19.0 % and a CBR of 52.4 % when combining RECIST and CA 125 criteria. The overall survival after single agent AEZS-

108 observed in this study was 12 months and compared favorably to the survival observed following topotecan (9.5 months) and doxorubicin (8.2 months) [11].

Endometrial cancer. AEZS-108 was studied in 43 advanced or recurrent endometrial cancer patients with LHRH positive tumor status. Given as a 2-hour IV infusion at 267 mg/m^2 every 3 weeks, it was shown to be active based upon an ORR of 30.2 % and a CBR of 69.8 %. The overall survival of 15 months after single agent AEZS-108 observed in this study was similar to the 15.3 months reported in the literature for triple combination chemotherapy [10].

A total of 43 patients were exposed to AEZS-108. The majority (97.7 %) of patients were Caucasian and the mean age was 66 years (range = 25 to 87 years). The mean time since diagnosis was 34 months (range = 7 to 151). All patients had undergone prior surgery for their disease while 69.8 % of the patients received prior radiotherapy. Ten patient out of 43 (23.3 %) received chemotherapy prior study entry, which consisted of the combination of platinum/paclitaxel in eight patients (18.6 %).

In the ITT population, a total of 15 responses (3 CR and 12 PR) were reported by investigators for an objective response rate (ORR) of 34.9 % and a clinical benefit rate (CBR) of 76.7 %. A total of 13 responses (2 CR + 11 PR) were determined by the external reviewer, for an ORR of 30.2 % and a CBR of 69.8 % (see Table below).

Tumor response	**Per investigator (N = 43)**	**Per reviewer (N= 43)**
Complete response (CR)	3 (7.0 %)	2 (4.7 %)
Partial response (PR)	12 (27.9 %)[a]	11 (25.6 %)[a]
Stable disease (SD)	18 (41.9 %)	17 (39.5 %)
Progressive disease (PD)	7 (16.3 %)[b]	7 (16.3 %)[b]
Objective response rate (CR + PR)	15 (34.9 %)	13 (30.2 %)
Clinical benefit rate (CR + PR + SD)	33 (76.7 %)	30 (69.8 %)
Not evaluable	3[c, d]	6[c, d, e]

[a]: Partial response not confirmed at a subsequent time point for the 3 patients.

[b]: In 1 patient, the investigator reported SD at cycle 1 in the CRF. As this tumor assessment had not been completed post-treatment, best overall response was based on cycle 4 assessment and was considered PD.

[c]: Symptomatic deterioration or death due to malignancy prior to cycle 2: 2 patients

[d]: Non-cancer death prior to cycle 2: 1 patient

[e]: Tumor assessments not evaluable per reviewer: 3 patients.

ORR and CBR in the per protocol population (n = 42) were not significantly different from the ITT population.

The median TTP as reported by the investigators was approximately 7 months. The median OS was 15 months.

1.3 Rationale for the present study

Selection of doxorubicin as comparator drug

In recent years, there has been a trend towards use of carboplatin/taxane for first line chemotherapy, so that doxorubicin whether as non-liposomal or pegylated liposomal doxorubicin (PLD) formulation is increasingly used in second line chemotherapy. Moderate response rates, however, have been reported for PLD when used in patients with prior chemotherapy (9 %) [16], but also in patients without prior chemotherapy (11.5%) [14], which could have been due to the selection of patients with less favorable prognosis for the latter trial [19].

Based on the reported moderate activity of PLD when used for second line therapy of endometrial cancer, non-liposomal doxorubicin has been selected as comparator drug in this trial.

The selection of doxorubicin as comparator drug in this trial implies that prior use of doxorubicin for advanced/recurrent disease is excluded.

Clinical assumptions underlying the statistical planning and sample size estimate

This study is planned to include patients who have relapsed or progressed on or after platinum/taxane-based chemotherapy. Therefore, the statistical plans for the present study are based on the following considerations.

Overall survival of endometrial cancer patients after use of doxorubicin in first line therapy was found at 7 months [1] and 9 months [20]. While shorter survival could be assumed if the drug is used in pretreated patients, better knowledge on the use of rescue treatments and improved patient care could lead to similar overall survival as seen in previous (first line chemotherapy) study. For comparison, median overall survival in a recent Phase II study of ixabepilone in pretreated patients was found at 8.7+ months [5]. Thus, the current study is planned under the assumption of a 9 month overall survival for the control arm.

Median OS in the recent Phase II study of AEZS-108 was 15 months; however, only 8 patients in this study were pretreated with a platinum/taxane regimen. The best response in the platinum/taxane pretreated patients included 1 CR, 1 PR, and 3 SD, corresponding to ORR of 25% and CBR of 62.5%. While this subset of patients is too small to reliably estimate an OS duration, an OS duration of 12 months was thought to be an estimate to be used in the sample size estimate for this study. If achieved, this would represent a clinically important benefit, being a 33% improvement over the anticipated survival in the control group.

Justification for the inclusion of patients without prior characterization of LHRH receptor status

The proportion of endometrial cancers reported to express or over express LHRH receptors varies between different studies and assays used. Percentages higher than 80 % have been reported in the literature [17, 21, 22]. So far, no standard assay or uniform criteria have been established for the quantification of LHRH receptor expressing cells or for the degree of expression or overexpression within given cells. In addition, antibodies used in

immunohisto-chemistry-based assays have been found to show variable specificity [unpublished data, data on file].

Thus, a new assay for the quantification of LHRH receptor expressing cells in endometrial cancer specimens is being developed. Reevaluation of tissue specimens from patients who have been treated with AEZS-108 in previous studies may be considered to compare the receptor classification between the new assay and previously used assays. However, as these clinical studies included patients selected for LHRH receptor expression, treatment results are only available for patients whose tumors had been classified as LHRH receptor-positive.

In order to establish the predictive value of the receptor assay, clinical results should be required from a study population including both patients with high and low degree of receptor expression, so that treatment outcome can be compared for patients with different extent of receptor expression.

For this reason, the present study is planned to include patients irrespective of the LHRH receptor status (‘all-comers’ approach). By this approach, also patients with minimal or without detectable LHRH receptor expression in their tumor cells could receive treatment with AEZS-108. In such patients, apart from a possibly low level of not receptor-mediated uptake of AEZS-108, free doxorubicin, which is gradually being released from AEZS-108, will be available for cellular uptake and thus confer therapeutic activity. The proportion of patients entering the study with LHRH receptor-negative tumors is expected to be low, based on the finding that 61 of 66 (92.8%) specimens were classified as LHRH receptor positive [Emons/Gründker, unpublished data].

Regarding the uncertainty of LHRH receptor classification with currently available and previously used assays, the demonstration of a relationship between extent of receptor expression and therapeutic response in this trial would be the ultimate clinical proof for the targeting concept and serve as a component of the validation work for the assay and its use as a companion diagnostic.

2 OBJECTIVES

Primary:

1. Compare the overall survival of patients treated with AEZS-108 to the OS of patients treated with doxorubicin

Secondary:

1. Compare efficacy based on progression-free survival (PFS), overall response rate (ORR), and clinical benefit rate (CBR).
   Subgroup analyses of efficacy parameters in relation to tumor LHRH receptor expression.
2. Compare safety.
3. Determine the impact of these regimens on patient-reported quality of life during and for up to 1 year after completion of study treatment.
4. Assess the pharmacokinetics and exposure-response relationships of AEZS-108, doxorubicin and doxorubicinol in a PK sub-study at selected sites and by sparse PK sampling, respectively.
5. Assess the acute effects on electrocardiographic parameters (e.g., QT/QTc interval) within PK sub-study.

3 ETHICS

The study will be conducted in agreement with the protocol and the following directives and guidelines:

- Declaration of Helsinki (Seoul, Korea, October 2008).
- Note for guidance on Good Clinical Practice (ICH-E6: CPMP/ICH/135/95 or 62 FR 25692).
- Guidance for Industry “E14 Clinical Evaluation of QT/QTc Interval Prolongation” (FDA, October 2005, ICH).
- Guidance for Industry “Exposure-response relationships” (FDA, April 2003).
- Guidance for Industry “Population pharmacokinetics” (FDA, February 1999).
- Applicable national rules and regulations.
- Standard Operating Procedures of Aeterna Zentaris.

3.1 Benefit / risk considerations

No standard of care or approved drugs are available for patients with endometrial cancer failing on or after first line chemotherapy for advanced/recurrent disease if this comprised platinum/taxane-based combination chemotherapy. In prior studies, it has been shown that, patients with endometrial and ovarian cancer who failed after or were resistant to platinum/taxane-based chemotherapy, including combinations, still responded to AEZS-108.

Although the investigational drug AEZS-108 is a targeted drug that is expected to enter cells bearing preferentially LHRH receptors, the study is being conducted in patients who will not be selected for expression of this specific target. Ultimately, a patient whose tumor cells do not express LHRH receptors could have a higher uptake of doxorubicin if it was administered as free doxorubicin, not coupled to the LHRH analog. In the Phase II study of AEZS-108, 92.8% of the endometrial cancer specimens analyzed during prescreening had been classified as receptor positive, so that only about 7% of the patients who might have entered the study if the receptor assay had been omitted. No correlation of the degree of receptor expression and the tumor response was noted in this earlier study. Accordingly, even patients with tumors classified as LHRH receptor negative – with the former assay - could have a chance to benefit from treatment with AEZS-108. Ultimately, since doxorubicin is being gradually released during and after the infusion of AEZS-108, a patient with an LHRH receptor negative tumor has the chance to benefit from the uptake of hydrolytically released doxorubicin by the tumor.

3.2 Protection of patients

Before initiation of the trials, the study protocol will be reviewed by the competent independent ethics committees (IEC). The study will be notified to the competent authorities.

The patients will be informed both verbally and in writing about the nature of the study, the anticipated benefits and risks, the discomfort to which they may be exposed, and their right to interrupt their participation at any time on their own free will. They will confirm their consent in writing prior to inclusion. The subject's informed consent form will be reviewed and approved by the IEC/IRB. For investigator's obligations regarding patient information and consent, see Section 10.2.

The Sponsor will insure adequate insurance coverage in the event of patient injury resulting from participation in the trial. Patients should be instructed to immediately notify the investigator of any injury that may have been caused by participation in this trial. A copy of the insurance conditions is included in the investigator's file.

4 STUDY DESIGN

This is an open-label, randomized, active-controlled, two-arm Phase III study to compare the efficacy and safety of AEZS-108 and doxorubicin. The study will include about 500 patients with advanced, recurrent or metastatic endometrial cancer who have progressed and who have received one chemotherapeutic (i.e., cytotoxic) regimen containing platinum **and** taxane (either as adjuvant or first line treatment).

Patients will be centrally randomized in a 1:1 ratio to receive treatment with either AEZS-108 (Arm A) or doxorubicin (Arm B).

During ongoing treatment, response will be evaluated every 3 cycles; earlier reassessments should be scheduled to verify a response (at least 4 weeks after first observation of the response) or in case of suspected progression. Patients, who have gone off-treatment for other reason than progression, will be reassessed every 12 weeks until progression. All patients will be followed-up for survival.

On a regular basis, at intervals no longer than 6 months, results from safety analyses will be submitted to an independent Data and Safety Monitoring Board (DSMB) that will advise the Sponsor of potentially critical findings.

The final analysis will be performed after about 384 deaths have been observed. There will be two planned interim analyses; the first will be for futility only, the second will be for safety and efficacy.

Based on the availability of the assay for LHRH receptor expression in tumor specimens, subgroup analyses stratified for extent of LHRH receptor expression will assess the predictive value of the LHRH receptor assay.

A sub-study, at selected sites, will investigate the pharmacokinetics of AEZS-108, doxorubicin and doxorubicinol and assess the acute effects on electrocardiographic parameters.

Sparse PK sampling will be performed, at all sites where feasible, to explore exposure-response relationships between AEZS-108 and its metabolites and measures of safety and efficacy.

5 PATIENT SELECTION

5.1 Inclusion criteria

To be eligible for this study, a patient must meet all of the following criteria:

1. Women ≥ 18 years of age
2. Histologically confirmed endometrial adenocarcinoma of any subtype.
   a) Endometrioid carcinoma
      i. Variant with squamous differentiations
      ii. Villoglandular variant
      iii. Secretory variant
      iv. Ciliated cell variant
   b) Mucinous adenocarcinoma
   c) Serous adenocarcinoma
   d) Clear cell adenocarcinoma
   e) Mixed cell adenocarcinoma
   f) Squamous cell carcinoma
   g) Transitional cell carcinoma
   h) Small cell carcinoma
   i) Undifferentiated carcinoma
3. Advanced (FIGO III or IV), recurrent or metastatic disease.
4. Measurable or non-measurable disease that has progressed since last treatment.
5. Patients with advanced, recurrent, or metastatic endometrial cancer who have received one chemotherapeutic regimen with platinum **and** taxane (either as adjuvant or as first line treatment) and who have progressed.
6. Availability of fresh or archival FFPE tumor specimens for analysis of LHRH receptor expression

5.2 Exclusion criteria

A patient meeting any of the following criteria will not be eligible for this study:

Safety concerns:

1. ECOG performance status > 2.
2. Inadequate hematologic, hepatic or renal function
   - thrombocyte (platelet) count: < 100 x 10^9/L;
   - absolute neutrophil count (ANC): < 1.5x 10^9/L;
   - hemoglobin: < 5.6 mmol/L (< 9 g/dL);
   - ASAT, ALAT, AP: > 2.5 times upper limit of normal range (ULN) (> 5x ULN if clearly related to liver metastases);
   - creatinine, bilirubin: > 1.5x ULN.
3. Red blood cell transfusion within 2 weeks prior to anticipated start of study treatment.
4. History of myocardial infarction, acute inflammatory heart disease, unstable angina, or uncontrolled arrhythmia within the past 6 months.
5. Impaired cardiac function defined as left ventricular ejection fraction (LVEF) < 50 % (or below the study site's lower limit of normal) as measured by MUGA or ECHO. (LVEF measurements dating back up to 8 weeks will be acceptable in the absence of intercurrent use of potentially cardiotoxic treatment or cardiac medical history).
6. Concomitant use of prohibited therapy (as specified in Section 6.3.2).
7. Chemo-, immune-, or hormone-therapy within 5 elimination half-life times or 4 weeks prior to randomization, whichever is the shorter. Radiotherapy (including pre- or post-operative brachytherapy) within 4 weeks prior to randomization.
8. Previous anthracycline-based chemotherapy (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone and valrubicin), in any formulation.
9. Anticipated ongoing concomitant anticancer therapy during the study.
10. History of serious co-morbidity or uncontrolled illness that would preclude study therapy, such as active tuberculosis or any other active infection.
11. Brain metastasis, leptomeningeal disease.
12. Pregnant or lactating female or female of childbearing potential not employing adequate contraception. Women of childbearing potential must agree to employ adequate contraception until 6 months after the last dose of study drug defined as
    - complete abstinence; (Note: acceptable only as "true abstinence", i.e. when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence, (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
    - any intrauterine device (IUD) with published data showing that the lowest expected failure rate is < 1 % per year; or
    - any other methods with published data showing that the lowest expected failure rate is less than 1 % per year.
13. Subjects with known hypersensitivity to peptide drugs, including LHRH agonists.

Lack of suitability for the trial:

22. Malignancies arising from the uterine cervix

23. Uterine sarcomas or mixed epithelial and mesenchymal tumors including carcinosarcoma, adenosarcoma, or carcinofibroma
14. Receipt of 2 or more prior cytotoxic chemotherapy regimens for advanced, recurrent, or metastatic endometrial cancer.
15. Prior treatment with AEZS-108.
16. Use of LHRH agonist or antagonist treatment within 6 months prior to randomization (see Appendix 5 for examples of drug names).
17. Malignancy within last 5 years except non-melanoma skin cancer.
18. Any concomitant disease or condition that would interfere with the subjects' proper completion of the protocol assignment.
19. Concomitant or recent treatment with other investigational drug (within 4 weeks or 5 elimination half-life times prior to anticipated start of study treatment).

Administrative reasons:

20. Lack of ability or willingness to give informed consent.
21. Anticipated non-availability for study visits/procedures.

5.3 Withdrawal criteria

A patient discontinued of study procedures prior to randomization will not be considered as a withdrawal but as a "screen failure", irrespective of the reason for the discontinuation.

Withdrawal is to be understood as a permanent removal of a patient from planned study procedures after randomization. This will include both,
(i) the premature discontinuation of study treatment before delivery of the planned number of treatment cycles (for AEZS-108) or of the maximum allowed cumulative lifetime dose (for doxorubicin), and
(ii) the discontinuation of follow-up before the primary end point of the study has been reached or the study has been closed.

At any time, patients may be withdrawn from the study at their own request or on the basis of the investigator's clinical judgment. However, patients who request withdrawal will be strongly encouraged to complete follow-up assessments.

Reasons for withdrawal from treatment and/or follow-up will be classified as follows:

- **Lack of efficacy:** the patient shows inadequate response to treatment (progressive disease) or deterioration.
- **Lack of tolerability:** unacceptably bad tolerability reported by the patient or observed by the investigator (e.g., failure to sufficiently recover from toxicity within 2 weeks of the scheduled day of the next cycle, cardiac adverse events judged as possibly related to study drug).
- **Cardiac toxicity:** defined as
    - reduction in LVEF to < 45 %;
    - reduction in LVEF by ≥ 15 % points from baseline value (e.g. from 70% to 55%);

- evidence of clinical congestive heart failure (CHF), confirmed by the investigator;
- myocardial infarction.

- **Intercurrent disease:** any disease or condition occurring during the trial that makes any further participation impossible judged as unlikely related to study drug or relationship not assessable.
- **Withdrawal of consent / non-compliance:** the subject/patient withdraws his/her consent or the patient is non-compliant with study procedures; it should be attempted to clarify whether an adverse event may have caused the withdrawal and, if so, amend the AE documentation accordingly.
- **Other reason(s):** reason for discontinuation not covered by any of the above criteria (e.g., patient moved out of the area, investigator's decision that discontinuation is in the best interest of the patient, priority of an alternative treatment option). Other reason(s) must be specified.

The investigator should also provide in the CRF a brief comment on each case of withdrawal.

5.4 Replacement policy

There will be no replacement of patients who have been withdrawn or who dropped out after randomization.

6 DESCRIPTION OF TREATMENTS

Subject will be randomly allocated to receive either:

- AEZS-108 - Investigational drug (Arm A)

  OR

- Doxorubicin – Comparator drug (Arm B).

Details related to AEZS-108 (Arm A) are presented in Section 6.1 while those related to doxorubicin (Arm B) are provided in Section 6.2. Information provided in Section 6.3 to Section 6.4 is applicable to both, Arm A and Arm B.

6.1 Investigational drug – AEZS-108

6.1.1 Description / general issues

Description: AEZS-108 is formulated as a powder (lyophylisate) and provided in glass vials containing 100 mg of the active substance, without additional excipients. The 100 mg vials are further packaged in boxes. Vials and boxes will be labeled as shown in a copy in the investigator's file.

Retest date, manufacturing date: Trial medication may not be used after a retest date specified on a drug product label. Replacement of such medication with new or relabeled medication, indicating the revised retest date, is required.

Where allowed by local regulations, the label of the trial medication will specify the manufacturing date. Such medication may not be used after the retest date, which is specified in the certificate of analysis.

Responsibility at the study center: The investigator is responsible for the appropriate storage and distribution of the investigational products and will observe the applicable regulations. The investigator may name a responsible person, e.g. pharmacist, to take care of the trial medication.

Supply: Trial medication will be shipped to a responsible person at the investigator's institution who will check amount and condition of the drug received and will return an acknowledgement of receipt to Aeterna Zentaris.

Storage: The trial medication can be stored in a refrigerator, at temperatures between 2 and 8 ºC, protected from light. The trial medication may not be used after the specified retest/expiry date.

Accountability: The responsible person at the study center has to account for all used and unused trial supplies of AEZS-108 and has to complete a *Medication Accountability List* that includes the following information:

- identification of patient (number and initials),
- date and quantity of drug dispensed,
- date and quantity of drug returned to Aeterna Zentaris.

At the end of the trial, or as directed, residual supplies and the completed *Medication Accountability List* will be returned to Aeterna Zentaris, a copy of the completed list will be retained in the Investigator's file.

The trial medication must not be used outside this protocol.

6.1.2 Reconstitution and administration

Reconstitution and dilution: Physiological saline (0.9 % NaCl solution) will be used as solvent for the reconstitution and dilution of AEZS-108 solution.

Four (4) mL of saline will be added per 100 mg vial, resulting in a concentration of 25 mg AEZS-108 per mL of the reconstituted solution.

The appropriate volume of reconstituted AEZS-108 solution will be diluted with physiological saline, such as to contain the desired amount of drug substance in an infusion volume of about 250 mL.

Stability in diluted solution: Not more than 1 hour should elapse between dissolution of the lyophylisate and the preparation of the solution for infusion. The diluted solution for infusion can be stored at room temperature, but must be completely infused within 7 hours after dissolution of the lyophilisate.

Administration (Infusion): The administration schedule is as follows:

Dose:	267 mg/m^2; For each treatment course, dose calculation will take into account the body surface area (BSA) as derived from the patient's height and current body weight. (Note: If the body weight is +/- 10% of the body weight measured at day 1 of the preceding cycle, the body weight measured at day 1 of the preceding cycle may be used for calculating the dose to be prepared in the pharmacy). Appendix 1 provides a nomogram and reference to online BSA calculators for the determination of the BSA.
Route:	Intravenous infusion over a period of about 2 hours
Frequency:	Every Day 1 of 21-day (3-week) cycles
Duration:	The proposed maximum duration is 9 cycles. An individual patient will be withdrawn from study as soon as disease progression indicates treatment failure or poor tolerability requires withdrawal. (see Section 5.3 for withdrawal criteria).
Premedication	Recommended prophylactic antiemetic: 8 mg dexamethasone (see Section 6.3)
Warning:	**Paravenous administration must be avoided:** In rabbits, paravenous injection resulted in inflammatory reaction and necrosis of muscle cells. **Extravasation** may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. In the case of extravasation during infusion, it should be treated according the guidelines for therapy of doxorubicin extravasates. In addition to general treatment procedures for cytostatic extravasates, dimethyl sulphoxide (DMSO) 99 % should be applied to the entire extravasation area every 3 - 4 hours for at least 14 days.

6.1.3 Treatment modifications / delay of treatment

Any deviation from the planned dosing schedule must be commented on in the CRFs.

Delay of re-treatment: Subsequent cycles of study treatment should not begin before a patient has recovered to CTCAE Grade 1 from a drug-related adverse event (i.e., causality at least possibly related) that the investigator feels is clinically significant. No treatment delay is required for alopecia or anemia for which supportive therapy should be given according to study sites's clinical practice (see also 6.3.1.3). Re-treatment may be postponed for up to 2 weeks. A patient who has not recovered within 5 weeks after the last dose should be withdrawn and followed up as required.

Dose reduction: Any of the following drug-related adverse events (i.e., causality at least possibly related) will require a dose modification, if its duration exceeds the indicated period:

- Grade 4 neutropenia [ANC < 500/mm^3] lasting 7 days or more

- Grade 3 febrile neutropenia lasting for more than 7 days
  [Grade 3 defined as: ANC < 1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥ 38 °C (100.4 °F) for more than one hour]
- Grade 4 febrile neutropenia (of any duration)
  [Grade 4 defined as: Life-threatening consequences; urgent intervention indicated]
- Grade 3 thrombocytopenia [Platelet count: < 50,000 – 25,000/mm^3] persistent at the scheduled time of re-dosing (i.e. blood sample on the day before re-dosing) and associated with a clinical risk of bleeding (presenting, e.g. as hemorrhagic diathesis: petechial rash, especially affecting tunica mucosa in oral cavity, gingival rash or petechial skin rash associated with prolonged bleeding time, e.g. in the Duke bleeding time test)
- Any other Grade 4 hematological toxicity (except for lymphocytopenia) lasting 7 days or more
- Grade 3 nausea/vomiting/diarrhea lasting 5 days or more despite optimal medical management.

If any of the above dose-limiting toxicities occurs and re-treatment is indicated after the toxicity has resolved to ≤ Grade 1 within the allowed period for a treatment delay, then dosing will be resumed with a dose reduction.

Dose Level	**AEZS-108 Dose (mg/m^2)**
Starting Dose	**267**
1st Dose Reduction (approximate 20 % reduction)	210
2nd Dose Reduction (approximate 40 % reduction)	160

The dose reduction is permanent; no dose re-escalation to the original dose should be permitted once a dose has been reduced. Only 2 dose reductions per patient will be allowed. Patients who cannot tolerate the lowest dose will be discontinued and may receive other treatments at the investigator's discretion.

Supportive therapy (see also Section 6.3.1): Hematopoietic growth factors or transfusion of blood components may be administered as needed, e.g. in case of a delayed hematological recovery or in case of hematological toxicities with a shorter duration than specified above for DLTs.

6.1.4 Emergency measures

A specific antidote in case of AEZS-108 overdose is not available. Close observation should be performed and adequate supportive care provided; adverse events/reactions should be treated symptomatically.

Adverse reactions that were observed under treatment with AEZS-108 at the proposed dosing schedule are summarized in the Section 1.2.2.

6.2 Comparator drug – Doxorubicin

Commercially available doxorubicin products approved for use at the investigator's site will be used for the treatment of patients randomly allocated to Arm B. The trade name of the product used will be documented in the CRFs.

6.2.1 Description / general issues

Dry powder formulations, as well as ready-to-use solutions for intravenous use are allowed. The selection is at the discretion of the investigator, in line with applicable rules or regulations at study site.

All applicable instructions, warnings, and precautions in the prescribing information of the product used will be followed. References below to specific sections of the Prescribing Information should be verified with the prescribing information of the product actually used.

6.2.2 Reconstitution and administration

See corresponding Sections of the Prescribing Information.

6.2.3 Treatment modifications / delay of treatment

Dosage scheme:	60 mg/m^2 by intravenous **bolus injection, 1-hour intravenous infusion**, or according to standard institution procedures, on Day 1 of 21-day (3-week) cycles Note: If the body weight is +/- 10% of the body weight measured at day 1 of the preceding cycle, the body weight measured at day 1 of the preceding cycle may be used for calculating the dose to be prepared in the pharmacy.
Dose adjustment: - Renal function - Hepatic function	(for starting dose) at GFR below 10 ml/min.: 75 % of calculated dose at serum bilirubin 1.2 to 3.0 mg/100 mL: 50 % of calculated dose; at serum bilirubin > 3.0 mg/100 mL: 25 % of calculated dose
Maximum duration / dose:	up to a cumulative lifetime dose of 550 mg/m^2
Treatment delay:	Subsequent cycles of study treatment should not begin before a patient has recovered to CTCAE Grade 1 from a drug-related adverse event (i.e., causality at least possibly related) that the investigator feels is clinically significant. No treatment delay is required for alopecia or anemia for which supportive therapy should be given according to study sites' clinical practice (see also 6.3.1.3). Re-treatment may be postponed for up to 2 weeks. A patient who has not recovered within 5 weeks after the last dose should be withdrawn and followed up as required.Note that some Prescribing Information cite the criteria used in study NSABP B-15, using a

doxorubicin/cyclophosphamide combination regimen: When necessary, the next cycle of treatment was delayed until the absolute neutrophil count was ≥ 1000 cells/mm^3 and the platelet count was ≥ 100,000 cells/mm^3 and nonhematologic toxicities had resolved.

Dose reduction: (for retreatment)

75 % of the starting doses for neutropenic fever/infection. Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Plasma bilirubin concentration (mg/dL)	Dosage reduction (from starting dose)
1.2 - 3.0	50 %
3.1 - 5.0	75 %

For further information on treatment modifications, see Sections Dosage and Administration of the Prescribing Information.

6.2.4 Emergency measures

See Sections Warnings and Overdosage in the Prescribing Information.

6.3 Concomitant therapy

All concomitant medications and therapies (prescribed and non-prescribed) must be recorded in the case report form, with trade name (generic name), route or formulation, dosing scheme, the indication and start and stop dates of administration. Any change during the study should be documented as well.

6.3.1 Permitted therapy

6.3.1.1 Antiemetics

Vomiting was not a dose-limiting toxicity in the phase I clinical trial with AESZ-108. In phase II clinical trials completed in endometrial (n = 43) and ovarian (n = 42) cancer patients, no vomiting of grade 3 or 4 was observed following AEZS-108 at a dose of 267 mg/m^2.

According to the current ASCO guideline for “Antiemetics in Oncology” (2011) [3], AEZS-108 should be considered a chemotherapeutic agent with “low emetic risk” and therefore, before start of AEZS-108 infusion, prophylactic antiemetic treatment with 8 mg dexamethasone is recommended.

If additional symptomatic antiemetic treatment is needed, this should be started with an antiemetic with predominantly local/peripheral mode of action, like metoclopramide (Paspertin®), alizapride (Vergentan®).

If local/peripheral type antiemetics prove to be ineffective in a given patient, antiemetics with a predominantly central mode of action (5-HT3-antagonist, e.g. ondansetron (Zofran®)) will be used.

Antiemetics that were started as symptomatic treatment should also be given as prophylactic treatment in subsequent treatment cycles of the same patient.

6.3.1.2 Anti-allergic treatment

In case of an allergic reaction, treatment should consist of a step-by-step approach of general measures, such as adequate shock positioning, volume substitution, and the administration of appropriate drugs like epinephrine (0.1 to 1.0 mg), H_1-and H_2-receptor antagonists (dimetidene 4.0 to 8.0 mg, cimetidine 200 to 400 mg), and corticosteroids (prednisolone 0.5 to 1.0 g).

In patients that have experienced an allergic reaction during treatment with AEZS-108, prophylactic anti-allergic medication (like combined application of dimetidene and cimetidine) should be administered in subsequent treatment cycles.

6.3.1.3 Other

The following are permitted:

- In case of a delayed hematological recovery, hematopoietic blood components may be administered as needed.
- Colony stimulating factors should not be administered prophylactically during the first cycle of AEZS-108 or doxorubicin. From cycle 2 onwards, prophylactic use is at the discretion of the treating physician.
  Therapeutic use of colony stimulating factors in patients with hematotoxicity is permitted in any cycle.
- Supportive and palliative treatment without an anticancer effect (nutritional, transfusional support, pain control, bisphosphonates for bone metastases, etc.).

6.3.2 Prohibited therapy

Concomitant medication and treatments that may not be administered are:

- concomitant anticancer therapies (including treatment with another investigational drug and chemo-, immune-, hormone-, or radiotherapy, but excluding irradiation of non-indicator lesions for symptom relief),
- live vaccines
- amiodarone
- sotalol.

6.3.3 Interaction with other medicinal products and other forms of interaction

AEZS-108 may interact with other medicinal products in the same manner as doxorubicin. Therefore, based on doxorubicin's Prescribing Information, the following is a list of drugs

(other than those listed in section 6.3.2) potentially requiring precautions also when used with AEZS-108:

- Amphotericin B
- Antiepileptic drugs such as carbamazepine, phenytoin, valproate
- Cardioactive drugs, such as calcium channel blockers(e.g. verapamil)
- Cyclosporin
- Cimetidine
- Clozapine
- Digoxin
- Heparin
- Hepatotoxic drugs
- Inducers of CYP450, such as rifampicin and barbiturates
- Inhibitors of CYP450, such as fluvoxamine, ciprofloxacin, gemfibrozil, fluconazole, bupropion, cinacalcet, fluoxetine, paroxetine, quinidine, indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin
- Progesterone
- Radiation therapy (preceding, concomitant or subsequent)
- Ritonavir
- Substances influencing the bone-marrow function such as amidopyrine derivatives, antiretroviral drugs, chloramphenicol, phenytoin, sulphonamides
- Uric acid lowering agents

Examples of precautions are monitoring of cardiac function, monitoring of hemato/hepato/nephrotoxicity and dose adjustment. The investigator is referred to doxorubicin's Prescribing Information to identify which precaution(s) must be applied specifically to each drug listed above also when used concomitantly with AEZS-108.

6.4 Follow-up treatment (no crossover after the end of study treatment)

For a patient who requires further treatment for her malignant disease, after the end of study treatment with AEZS-108 or doxorubicin, the selection and timing of such treatment is at the discretion of the investigator. As there is no standard of care treatment in these cases, he/she will take into account the current signs and symptoms of the disease and, where applicable, any persisting drug-related adverse events (i.e., causality at least possibly related).

A patient who fails on either study treatment will NOT be allowed to cross over to the alternative study treatment.

7 ASSESSMENTS

The following endpoints will be assessed:

1. Overall survival (primary efficacy endpoint).

2a Efficacy: progression-free survival (PFS), overall response rate (ORR = CR + PR), and a clinical benefit rate (CBR) will be evaluated as CR + PR + SD for at least 3 months.

2b. Safety: adverse events, clinical laboratory, ECG and LVEF.

2c. Quality of Life: EORTC QLQ30 + QLQ-EN24 questionnaires.

Pharmacokinetic and electrocardiographic parameters of the PK sub-study are described in APPENDIX 7 of the protocol.

Evaluation of exposure-response relationship and population pharmacokinetic evaluations will be described in the Statistical Analysis Plan.

7.1 Efficacy (RECIST)

Response and progression will be evaluated using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [6]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

During ongoing treatment, patients should be re-evaluated for response every 3 cycles (i.e. every 9 weeks).

The following text is a summary of RECIST 1.1.

7.1.1 Confirmatory Measurement

A subsequent scan must be obtained no earlier than 4 weeks following the initial documentation of an objective status of either complete response (CR) or partial response (PR).

Note: During ongoing treatment, the next scheduled follow-up measurement would be due after three more cycles, i.e., 9 weeks later in absence of treatment delays). In order not to miss the confirmation of the response, or if a patient will go off treatment, a separate imaging session should be scheduled, however, no earlier than 4 weeks after the previous imaging.

7.1.2 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

7.1.3 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as >10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will be considered measurable (and eligible as target lesion) if they have developed or progressed after the irradiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease (*not applicable in this study*), ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

7.1.4 Methods for Evaluation of Measurable Disease

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 4 weeks 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes) and 10 mm diameter as assessed using calipers (e.g. skin nodules). 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: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

Tumor markers *(not applicable in this study)*

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g. residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

7.1.5 Response Criteria

7.1.5.1 Evaluation of Target Lesions

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

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

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

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

7.1.5.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

7.1.5.3 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). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 1: Response for patients with measurable disease (i.e., target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: Tumor response for patients with non-measurable disease (i.e., non-target disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

7.1.6 Duration of Response

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

7.1.7 Progression-Free Survival (PFS)

PFS is defined as the time elapsed from randomization to the date of documented progression or death, whichever comes first. For surviving patients without progression who begin alternative treatment, PFS will be censored at the last date of documented progression-free status prior to starting alternative treatment. Similarly, losses to follow up will be censored at the last date of documented progression-free status.

7.1.8 Overall response rate (ORR)

ORR i.e. overall response rate is defined as the sum of the complete and partial response rate as detailed in Section 7.1.5.

7.1.9 Overall Clinical benefit rate (CBR)

CBR is defined as the sum of the complete response and partial response and stable disease rate as detailed in Section 7.1.5.

Additionally, we define clinical benefit as non-progression at 9 weeks with no toxicity requiring termination of treatment.

7.1.10 Overall survival

Overall survival (OS) is defined as the elapsed time from randomization to death from any cause. For surviving patients, follow-up will be censored at the date of last contact.

7.2 Safety

7.2.1 Adverse events

7.2.1.1 Definitions

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

A Documentation rules for abnormalities in laboratory finding, vital signs, ECG etc. are specified in Section 7.2.1.3.

B This will also include intercurrent diseases and accidents observed during treatment period as well as corresponding events during drug-free periods, under placebo or in a reference group receiving drug or non- drug therapy.

Serious adverse event (SAE) means any untoward medical occurrence that at any dose[A]:

- results in death,
- is life-threatening[B],
- requires inpatient hospitalization or prolongation of existing hospitalization[C],
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect or
- is another medically important condition[D].

[A] All events that meet the definition of an SAE but, in the opinion of the treating investigator, are clearly expected from the patient's disease or related to disease progression (i.e., there exists no reasonable possibility that they were caused by the study drug) should be recorded on the case report forms only and do **not** require the reporting as an SAE (as defined in protocol Section 7.2.1.4). This will also apply to patient's death that is clearly attributed to the underlying malignant disease.

[B] The term "life-threatening" in the definition of "serious" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

C. Hospitalization for elective treatment of a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Admittance to an emergency room for observation without being admitted to the hospital may be considered an AE, but is not considered as an SAE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Hospitalizations for symptoms of progressive disease are not considered an SAE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious.

D Medically important conditions that may not result in death, be life threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse [Ref: Federal Register §312.32 IND safety reports].

Please note: The term "severe" is often used to describe the intensity (severity) of an event (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or vital functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Severity Grading
The NCI Common Terminology Criteria for Adverse Events (version 4.03 or subsequent ones) are to be used for the grading of severity of symptoms and abnormal findings. A copy of the document is included in the investigator's file (see also: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

For adverse events not covered by the NCI-CTCAE grading system, the following definitions will be used:

- **Grade 1 - Mild**: awareness of sign, symptom, or event, but easily tolerated
- **Grade 2 - Moderate**: discomfort enough to cause interference usual activity and may warrant intervention
- **Grade 3 - Severe**: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention
- **Grade 4 - Life-threatening**: immediate risk of death (Note: will require reporting as an SAE)

Causality assessment
The investigator will assess the causal relationship of an AE/SAE to the study drug using the following categories and definitions.

- **Likely** (at least 3 of the following conditions must apply):
  - AE had a reasonable temporal relationship to administration of trial medication;
  - AE could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions;
  - AE followed a known pattern of response to the trial medication;
  - AE disappeared or decreased with reduction in dose or cessation of the trial medication.
- **Possible** (at least 2 of the following conditions must apply):
  - AE had a reasonable temporal relationship to administration of trial medication;
  - AE could not readily have been produced by the subject's clinical state;
  - AE could not readily have been due to environmental or other interventions;
  - AE followed a known pattern of response to the trial medication.
- **Unlikely** (at least 2 of the following conditions must apply):
  - AE did not have temporal relationship to administration of trial medication;
  - AE could readily have been produced by the subject's clinical state;
  - AE could have been due to environmental or other interventions;
  - AE did not follow known pattern of response to the trial medication;
  - AE did not reappear or worsen with reintroduction of the trial medication.
- **Unrelated:**
  - AE was clearly due to extraneous causes (e.g. underlying disease, environment).

7.2.1.2 Procedures in case of adverse events

Throughout the study, the patient will be questioned and/or examined by the Investigator or his/her designee for evidence of adverse events. The questioning of patients with regard to the possible occurrence of adverse events should be as non-specific as possible. However, given that it is the site's responsibility to follow up all AEs, specific questions related to previously reported AEs with regard to their resolution or continuation must be asked.

All adverse events occurring during a study have to be documented, regardless of any assumption of a causal relationship, on the respective AE CRF. All events that occurred during the screening period should be documented as medical history. The investigator should ensure, e.g. by telephone call to the trial subject, to record all events that occurred within 28 days after the last exposure to study drug.

Documentation of adverse events includes date of onset and offset, pattern, duration, severity, impact, actions taken, seriousness, and outcome. The investigator should also

evaluate the probability of a causal relationship of the adverse event to the study medication as likely, possible, unlikely, or unrelated. Information provided in the Investigator's Brochure may support this evaluation.

7.2.1.3 Documentation of routine safety parameters

A value outside the normal or reference range in a routine safety assessment, such as clinical laboratory, vital signs, or ECG, may signify an adverse finding. If the investigator considers the abnormality as clinically significant/relevant, as defined below, he should also record this on the CRF Adverse Events [Note: A clinically significant abnormality observed prior to first administration of study treatment should be recorded as update of the CRF Medical History]. If the findings contribute to a clinical diagnosis, such as hepatitis in case of increased liver enzymes, this diagnosis should be recorded as adverse event.

An abnormality must be considered as clinically significant, if

- it represents a serious adverse event, or
- it led to premature discontinuation of the study, or
- it required a therapeutic measure, or
- in the judgment of the investigator - it indicates a medically relevant condition or risk, without meeting any of the above criteria.

7.2.1.4 Reporting of serious adverse event

The investigator must report serious adverse events (SAE) occurring or observed from the day of first administration of the investigational drug on and until 4 weeks after last administration of the investigational drug (development of impaired cardiac function (ex. ≥ grade 4 left ventricular systolic dysfunction) within 1 year after last administration of study drug should also be reported as an SAE); see page 2 for contact persons and email/phone/fax numbers. As soon as possible, but in no case later than 24 hours after the SAE has been noted, the *"Serious Adverse Event Report"* form *(copies included in the Investigator's File)* should be sent by email, whether or not complete information is available within this period. In case of incomplete information, the investigator has to provide follow-up information as soon as possible, again using the SAE report form.

Regarding hospitalization, please refer to Section 7.2.1.1, footnotes A and C for circumstances that will determine the consideration as SAE and need for reporting on an SAE form to AEZS drug safety.

All events that meet the definition of serious but, in the opinion of the treating investigator, are clearly expected from the patient's disease or related to disease progression (i.e., there exists no reasonable possibility that they were caused by the study drug) should be reported on the case report forms and do not require immediate reporting on an SAE form.
This will also apply to patient's death that is clearly attributed to the underlying malignant disease.

Reports will be evaluated by Aeterna Zentaris and authorities will be informed according to national or international regulations. The same information will also be made available to principal investigators of other currently ongoing trials with the same study medication.

7.2.2 Clinical laboratory tests

The following clinical laboratory tests will be performed in the laboratory of each center. Clinical laboratory tests will comprise the following parameters:

Panel name	Laboratory parameters included
Hematology	leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes (platelets); differential white blood cell count (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
Chemistries	
- Enzymes	AST/SGOT, ALT/SGPT, gamma-GT, alkaline phosphatase, LDH
- Substrates	total protein, total bilirubin, creatinine, urea, uric acid
- Electrolytes	sodium, potassium, calcium
Urinalysis	glucose*, protein*, microalbumin**
Hormones	luteinizing hormone (LH), follicle stimulating hormone (FSH)
Pregnancy test	ß-HCG (in serum; for women of childbearing potential only)

* In case there is no possibility for evaluation of the parameters provided above semiquantitative dipstick analysis will be accepted

** In cases where 24-hour urine is not available to determine microalbumin, the microalbumin/creatinine ratio or microalbumin-specific urine sticks may be used instead.

For each value outside the normal range, the investigator must classify the clinical significance/relevance of the abnormality following the criteria defined above, in Section 7.2.1.3.

7.2.3 Vital parameters, body weight, and performance status

Vital parameters to be recorded comprise systolic and diastolic blood pressure, and pulse.

Body weight shall be recorded in kg (rounded to closest integer). Note: the current body weight shall be used for the estimation of the body surface area (Appendix 1), as the basis for the total dose to be administered. (Note: If the body weight is +/- 10% of the body weight measured at day 1 of the preceding cycle, the body weight measured at day 1 of the preceding cycle may be used for calculating the dose to be prepared in the pharmacy).

Performance status will be recorded according to the ECOG/Zubrod scale (see Appendix 2).

The investigator should comment in the respective section of the CRF on a change compared to screening that is considered as clinically relevant. Such comment should - as far as possible - provide some explanation for the change. For obligations regarding documentation of abnormalities in vital signs as AE see Section 7.2.1.3.

7.2.3.1 ECG

The ECG will be recorded as scheduled in the flow-chart by means of a 12-lead (I, II, III, aVR, aVL, aVF, V_1-V_6) ECG system over a duration of 10 sec while the subjects will rest in supine position. The chart speed will be set at 25 mm/sec. The ECG patterns will be analyzed qualitatively with particular emphasis on changes in the T-wave duration and

morphology. The following will be computed by the ECG machine: heart rate, time intervals such as PQ/PR, QRS and QT interval, the heart rate corrected QTc interval calculated according to Bazett's formula (QTcB = QT/√RR) or Fridericia's formula (QTcF = QT/^{3}√RR), where QTc is the QT interval corrected for rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds.

The investigator should comment on the CRF on any deviation from normal that is considered clinically significant/relevant. If a finding is considered as clinically significant as defined in above, in Section 7.2.1.3, it must also be documented on the CRF Adverse Events.

For recording and evaluation of ECGs within the pharmacokinetic sub-study, refer to Appendix 7 of the protocol.

7.2.3.2 Left ventricular ejection fraction (LVEF)

Cardiac function will be monitored by either echocardiography (ECHO) or radionuclide ventriculography (RNV) / multigated radionuclide angiography (MUGA). The technique used for assessment should be consistent throughout the trial for a given patient.

RNV/MUGA should be used where good quality ECHO images cannot be obtained from a patient, e.g., because of concomitant lung disease.

If test results indicate deterioration in cardiac function during the study, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage. Patients with LVEF < 30% are at significant risk of congestive heart failure. See Section 5.3 for withdrawal criteria.

7.3 Other

7.3.1 Characterization of LHRH receptor expression in tumor tissue

It is planned to determine the expression of LHRH receptors in patients' tumor specimens ('receptor status') and to correlate the receptor status with clinical outcome data.

An assay for LHRH receptor expression is currently under development and may become available prior to the end of patient recruitment. Therefore, archival FFPE specimens (blocks) must be retained at the site. Similarly, FFPE blocks must be prepared from any fresh biopsy material obtained during screening. Study sites will be instructed about the timing and specific conditions of the specimens to be submitted.

7.3.2 Quality of life (QoL)

QoL will be measured by the EORTC QLQ-C30 questionnaire [2, 9], supplemented by the Endometrial Cancer Module (QLQ-EN24) which is designed for patients with all stages of endometrial cancer treated with pelvic surgery, chemotherapy, radiotherapy or concomitant radio/chemotherapy [12].

Specimens of both questionnaires are provided in Appendix 6.

7.3.3 Pharmacokinetic investigations

Detailed instructions for the collection, processing, storage and shipment of samples for pharmacokinetic investigations will be provided in a separate manual.

7.3.3.1 Sparse PK sampling

Sparse PK sampling of AEZS-108-treated patients will be performed at all investigational sites where feasible. Sparse PK sampling is expected in one cycle, either Cycle 1 or alternatively in a subsequent cycle of ongoing patients. The windows for the sampling are defined as follows:

Sample #	Time Window
1	within 60 minutes before end of the 2-hour infusion
2	between 30 and 60 minutes after the end of infusion (EOI)
3	between 120 and 180 minutes after EOI
4*	between 4 and 6 hours after EOI

*) optional, depending on feasibility

7.3.3.2 PK sub-study

The pharmacokinetic sub-study will be conducted at selected investigational sites; it is planned to involve 40 patients, 20 patients from each study arm. Procedures are described in APPENDIX 7 of the protocol.

8 STUDY PROCEDURES

A flow chart of the study procedures is displayed on page 13.

8.1 Patient's informed consent and registration prior to screening

A patient who has been identified as a potential candidate for the study will be informed about the study, based on the IRB/IEC approved written patient information.

Each patient who has given written informed consent will be registered into an interactive web-based response system (IWRS) before starting study-specific screening procedures.

The IWRS will issue a unique, 4-digit patient number that will be used to identify the patient on all study-related documents and specimens.

8.2 Screening procedures (within 4 weeks before start of treatment)

The following information will be obtained and screening tests will be performed within 28 calendar days before start of study treatment, i.e., Cycle 1 Day 1:

- **Medical history** and concomitant diseases (general and cancer-related history including prior treatment)

- **Clinical assessments** (physical examination, ECOG performance status and vital signs with height, weight, blood pressure, pulse)
    - **Clinical laboratory (**hematology, chemistries, urinalysis, hormones, pregnancy test (in serum) for women of childbearing potential)
- **Cardiac function:**
    - 12-lead electrocardiogram (ECG)
    - Left ventricular ejection fraction (LVEF): Echocardiogram or MUGA
      Note: In absence of intercurrent chemotherapy or cardiac medical history, results dating back up to 8 weeks will be acceptable.
- **Tumor imaging** (CT or MRI): Appropriate radiographic procedures to document extent of disease
  Note: For a given patient, the same imaging method must be used at screening and at follow-up assessments.
- **Quality of Life:** EORTC questionnaires
- **Tumor tissue specimens for LHRH receptor assay:** FFPE archival tumor specimen or – where available – FFPE fresh biopsies obtained during screening will be retained for later analysis.

Patients who are found to be ineligible will be registered in the IWRS as "Screen failure". The reason for screen failure will be captured categorically. Apart from demographic patient characteristics, no other detailed screening data will be captured.

8.3 Randomized allocation of study treatment

Patients who meet the eligibility criteria will be randomly allocated by central randomization in a 1:1 ratio to receive either AEZS-108 (Arm A) or doxorubicin (Arm B).

Start of study treatment (Cycle 1 Day 1) should be scheduled for the nearest feasible date, to ensure that screening investigations, in particular laboratory investigations or measurements, have been performed within 28 days prior to treatment start.

8.4 Procedures during treatment

8.4.1 Procedures on Cycle 1 Day 1 (date of first study treatment)

After randomization, but prior to first administration of study treatment, each patient will have the following assessments and tests:

- **Interval history** and symptom-directed examination
  Findings to be recorded as Medical History / Concomitant Disease/Condition
- **Clinical assessments** (including ECOG performance status, blood pressure, pulse, and weight for BSA and dose calculation)
- **Clinical laboratory** tests (hematology, chemistries, urinalysis)
- **Eligibility criteria review**
  In the absence of new findings that would violate any of the eligibility criteria,

except for Day 1 clinical laboratory tests, the patient may receive the allocated study treatment.

- **Study treatment**
  Administration of allocated study medication at the recommended starting dose.
- **Sparse PK sampling (AEZS-108 treated patients only)**
  Blood collections within the following time windows:
  sample #1: within 60 minutes before end of the 2-hour infusion
  sample #2: between 30 and 60 minutes after the end of infusion (EOI)
  sample #3: between 120 and 180 minutes after EOI;
  sample #4 (optional): between 4 and 6 hours after EOI.

  A patient, in whom sparse PK sampling was not possible in Cycle 1, may have the samples taken at any subsequent cycle. It is not planned to have repetitive sparse sampling of the same patient during multiple cycles.
- **PK substudy (instead of 'sparse PK sampling', at selected investigational sites only)**
  Procedures related to the PK substudy are described in Appendix 7 of the protocol.

8.4.2 Weekly procedures during Cycle 1

Once weekly controls during Cycle 1 will include the following:

- **Clinical assessments** (including blood pressure and pulse)
- **Clinical laboratory** tests (hematology, chemistries, urinalysis)
- **Adverse event** recording.

Retreatment is planned in 3-weekly intervals, i.e. Day 1 of new cycle is corresponding to Day 22 of the previous cycle. In case of incomplete recovery from hematological toxicity or adverse events, re-treatment may be delayed for up to 2 weeks, i.e. with appropriate supplementary weekly controls on Day 29 and Day 35 (see Section 6.1.3).

8.4.3 Procedures on Day 1 of Cycle 2-9

It will be allowed to schedule tests up to 3 days before the planned Cycle Day 1, to ensure availability of safety-relevant results prior to dosing.

- **Interval history** and symptom-directed examination
  Adverse changes to be recorded as Adverse Events
- **Clinical assessments** (including ECOG performance status, blood pressure, pulse, and weight for BSA and dose calculation). Note: If the body weight is +/- 10 % of the body weight measured at day 1 of the preceding cycle, the body weight measured at day 1 of the preceding cycle may be used for calculating the dose to be prepared in the pharmacy.
- **Clinical laboratory** tests (hematology, chemistries, urinalysis, hormones)

- **Cardiac function:**
  - 12-lead electrocardiogram (ECG)
- **Study treatment**
  If dose-limiting toxicities have been observed in a previous cycle, the dose of the study treatment will be reduced in the next cycle (as well as in further cycles), as specified in Section 6.1.3 or 6.2.3.
- **Sparse PK sampling** (AEZS-108 treated patients only)
  A patient in whom sparse PK sampling was not possible in Cycle 1 may have the samples taken at any subsequent cycle. It is not planned to have repetitive sparse sampling of the same patient during multiple cycles.
  Blood collections within the following time windows:
  sample #1: within 60 minutes before end of the 2-hour infusion
  sample #2: between 30 and 60 minutes after the end of infusion (EOI)
  sample #3: between 120 and 180 minutes after EOI;
  sample #4 (optional): between 4 and 6 hours after EOI.

8.4.4 Procedures during Cycle 2-9

Depending on hematological toxicities and any safety issues observed during Cycle 1, scheduling of hematological controls and/or other investigations is at the discretion of the investigators. For tests performed by a laboratory not affiliated with the study site (e.g. mid-cycle controls by the patient's home doctor) copies of the external laboratory reports will be provided to the sponsor and results reported in the CRF.

Adverse findings in such controls/investigations/diaries that the investigator considers as clinically important/significant will be recorded as Adverse Event.

8.4.5 Procedures at the end of Cycle 3 and 6

The following assessments will be performed at end of Cycle 3 and Cycle 6, i.e. together with the assessments required to assure continuation of study treatment with Cycle 4 and Cycle 7, respectively.

- **Cardiac function:**
  - Left ventricular ejection fraction (LVEF): echocardiogram or MUGA

  Note: Recommended to be conducted also at end of Cycle 7 and 8 (i.e., before start of Cycle 8 and Cycle 9, respectively) for both arms. Results are to be captured on the eCRF if there is an abnormal finding.
- **Quality of Life:** questionnaires
- **Tumor imaging (CT or MRI):** evaluation of time-point response by comparison with target and non-target lesions defined at screening (baseline)

8.5 Procedures at end of study treatment

A patient who is going off study treatment (see Section 5.3) – will have the assessments/investigations specified below.

As an end-of-cycle assessment, it should be scheduled 3 to 5 weeks (Day 21 to 35) after the last dose. Additional visits/assessments may be indicated to follow-up unresolved adverse events.

- **Interval history** and symptom-directed examination
- **Clinical laboratory** tests (hematology, chemistries, urinalysis, hormones)
- **Cardiac function:**
  - 12-lead electrocardiogram (ECG)
  - Left ventricular ejection fraction (LVEF): Echocardiogram or MUGA
- **Quality of Life:** questionnaires
- **Tumor imaging (CT or MRI):** evaluation of time-point response by comparison with target and non-target lesions defined at screening (baseline)
- **Final evaluations:** best response, reason for discontinuation, investigator's overall judgment on tolerability of study treatment

8.6 Post-treatment follow-up

A patient developing signs of cardiac failure during post-treatment follow-up will have LVEF and ECG evaluated; a left ventricular dysfunction of CTCAE Grade 4 will be reported as an SAE.

8.6.1 Follow-up until progression

Whenever possible, a patient who has discontinued study treatment for other reason than progressive disease will be followed up at 3-monthly intervals until progression including the following assessments:

- **Clinical assessments** (including ECOG performance status, blood pressure, pulse)
- **Tumor imaging (CT or MRI):** evaluation of time-point response by comparison with target and non-target lesions at time of Best Response
- **Quality of Life:** questionnaires

Anticipated exceptions from follow-up will be “withdrawal of consent”, “lost to follow-up”, “patient moved”.

Follow-ups until progression will be suspended in patients in whom a new cancer treatment has been started without prior documentation of progressive disease. The start date of the new systemic therapy (or local therapy directed to lesions on which response assessment was based) will be documented.

8.6.2 Follow-up for survival

For patients going off study, survival information will be collected at 3-month intervals, telephone contact is acceptable.

9 STATISTICAL CONSIDERATIONS

The sections of the Statistical Considerations describe the statistical methods to be used to analyze the efficacy and safety. These methods may be revised and updated due to reasons such as regulatory requirements or need for further clarifications. The final analysis plan will be documented in a formal statistical analysis plan (SAP) that must be finalized before database lock. The SAP will include details on how variables will be derived, how missing data will be handled, and how censoring procedures will be applied to time to event related variables as well as the details on statistical methods to be used for safety and efficacy analyses. The final clinical study report will discuss deviations from the SAP, if any.

Unless otherwise stated, all analyses will be performed using SAS Version 9 and all hypothesis tests will be conducted at a two-sided significance level of 0.05.

Summary tabulations will display the number of observations, mean, standard deviation, median, minimum, maximum, and appropriate percentiles for continuous variables, and the number and percentage by category for categorical data. Summaries will present data by treatment arm and overall, if appropriate. The data listings will include all available efficacy and safety data.

9.1 Analysis populations

The following populations will be used for statistical analysis.

9.1.1 Intent-to-treat population

The Intent-to-Treat (ITT) population will consist of all randomized patients. Analyses of this population will assign patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

9.1.2 Safety population

The safety population will include all randomized patients who received at least one dose of study treatment. In the safety analyses, patients will be included in the treatment arm that they have actually received.

9.1.3 Per protocol population

The Per-Protocol (PP) population will include all randomized patients without major protocol deviations. What constitutes a major protocol deviation will be determined and documented prior to database lock. Protocol deviations will also be presented in the clinical study report.

9.2 Demographic and baseline characteristics

The two treatment arms will be assessed descriptively for comparability of demographic and baseline characteristics. Data to be evaluated will include at least age, race, and components of disease severity assessment.

9.3 Treatments and medications

9.3.1 Prior treatment for endometrial cancer

Use of prior treatment for endometrial cancer will be presented as frequency counts and percentages. Descriptive statistics for the number of prior lines of therapy will also be presented. Prior chemotherapy will be coded using the World Health Organization (WHO) dictionary and summarized by treatment arms for the safety population.

9.3.2 Prior and concomitant medications

All medications recorded on the CRFs will be coded using the WHO dictionary. Prior and concomitant medications will be summarized by treatment arm in the safety population by anatomical therapeutic chemical (ATC) class level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of study treatment. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of study treatment but no later than 30 days after the last administration of study treatment. Medications with start and stop dates that overlap the date of first administration of study drugs will be summarized as both prior and concomitant medications.

9.3.3 Study treatment

Study treatment exposure (e.g., number of treatment cycles, total drug exposed) will be summarized by treatment arm in the ITT and safety populations.

Treatment modifications will be summarized by treatment arm in the ITT and safety populations for each of the study treatments separately. The number and percentage of patients with doses delayed (withheld) and doses reduced, and reasons for these dose changes will be summarized by treatment cycle.

A summary of the number and percentage of patients receiving subsequent alternative anticancer therapy after discontinuation of study treatment will be presented by treatment arm in the ITT population.

9.4 Primary efficacy outcome

9.4.1 Definition

The primary efficacy outcome is overall survival (OS). Overall survival will be defined as the days between randomization and the date of documented death for any cause. For patients whose survival status cannot be determined, their OS data will be censored at the last documented date that the patient is confirmed to be alive.

9.4.2 Primary analysis

The primary efficacy analysis will be performed using the ITT population. The final analysis, which is event-based, will be conducted after approximately 384 randomized patients have died. In the primary analysis, a log-rank test with an overall two-sided Type I error rate of 0.05 after taking the interim analyses into account will be used to compare OS between the two treatment arms via a SAS lifetest procedure. Kaplan-Meier estimates will be used to calculate median OS and the 95 % confidence interval of the median OS. The proportion of patients alive at six and 12 months (from randomization date) and the 95 % confidence intervals for these estimated proportions, if appropriate, will be presented.

A Cox model with treatment effects will be used to estimate the hazard ratio and perform hypothesis testing. The estimated hazard ratio and the 95 % confidence interval of the hazard ratio will be presented.

9.4.3 Sensitivity analyses

The following sensitivity OS analyses will be performed:

1. Patients who changed treatment will be censored at the day the patient received the new treatment;
2. PP analysis.

Additional sensitivity analyses may be performed as appropriate.

9.4.4 Subgroup analyses

OS will also be analyzed for the following subgroups:

1. Age ($\leq$ 64 and > 64 years of age)
2. Staging (FIGO stage III or IV)

Additional subgroup analyses may be performed if appropriate. In particular, if the strength of the LHRH receptor expression can be classified, subgroup analyses based on the strength of LHRH receptor expression will be performed.

9.4.5 Exploratory analyses

Exploratory analyses to evaluate potential risks/benefits factors may also be performed.

9.5 Secondary efficacy outcomes

9.5.1 Progression free survival (PFS)

Progression-free survival will be defined as the days between randomization and the date of documented progression or death for any cause. Criteria for disease progression can be found in Section 7.1.7.

For patients whose progression status cannot be determined, their PFS data will be censored at the last adequate progression assessment date that the patient is confirmed to have no progression.

Hypothesis testing between the two treatment arms will be performed using a log-rank test.

For each treatment arm, the median time to progression will be estimated using the Kaplan-Meier method and the 95 % confidence interval of the median will be reported.

9.5.2 Overall response rate (ORR) and clinical benefit

The ORR for each treatment arm will be estimated as the proportion of responders, defined as a patient whose best overall response is PR or better during the treatment period. All responses must be confirmed at least 4 weeks after the initial response is seen. Tumor assessments will occur every 3 cycles (± 7 days) during ongoing treatment then every 3 months (± 7 days) thereafter while the patient is on study. The last assessment will occur either when progression is confirmed or when approximately 384 randomized patients have died

Hypothesis testing between the two treatment arms will be performed using a Mantel-Haenszel test. The odds ratio and 95 % confidence interval of the odds ratio will be presented.

Clinical benefit is defined as having stable disease or better lasting for at least 9 weeks. Clinical benefit rate will be analyzed using the same methods for the ORR analyses.

9.5.3 Quality of life

Change from baseline in Quality of life will be analyzed via an ANOVA model with treatment effect and baseline quality of life score. The treatment effect and treatment difference will be estimated and the 95 % confidence interval of the estimates will be presented.

9.6 Safety analysis

Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety analyses will be performed using the safety population. Safety variables will be tabulated and presented according to the treatment the patient actually received. Exposure to study treatment and reasons for discontinuation of study treatment will also be tabulated.

9.6.1 Adverse events

Each AE and SAE term reported will be mapped to a preferred term (PT) using the MedDRA dictionary. The investigator will classify the severity of AEs using the NCI CTCAE v4.03 and will assess the relationship of each event to study treatment.

All AEs and SAEs occurring on study will be listed by patient. The frequency and percentages of patients with treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and PT, where treatment-emergent is defined as any AE that:

- Occurs after randomization and through the follow-up of the last treatment cycle or, if an SAE, until the event has resolved or stabilized,
- Is considered treatment-related regardless of the start date of the event, or
- Is present before randomization but worsens in intensity.

TEAEs that are considered at least possibly related to study treatment will be tabulated as well as deaths, SAEs, and events resulting in treatment discontinuation.

At each level of summarization, a patient will be counted only once for each AE, SOC, or PT experienced within that level. In the summation for AE severity, within each level of AE, SOC, or PT experienced, the one with the highest severity will be included. In the summation for AE's relationship to the study drug, within each level of AE, SOC, or PT experienced, the one with the closest relationship to the study drug will be included.

9.6.2 Laboratory test results

Continuous laboratory tests will be summarized by treatment arm across time on study using descriptive statistics for actual values and for changes from baseline. Where applicable, shift from baseline in NCI CTCAE grade and by high/low flags (where NCI CTCAE grades are not defined) will be presented by treatment arm and time. The frequency of clinically significant abnormal laboratory values will be tabulated.

9.6.3 Other safety outcomes

9.6.3.1 Vital signs

Vital signs will be summarized by treatment arm across time on study using descriptive statistics for actual values and for changes from baseline.

9.6.3.2 ECG

Descriptive analyses of ECG findings and intervals for both absolute and results and changes from baseline parameters will be performed. This will be done using listings, tables, and graphs, where appropriate.

The analyses will include:

- Absolute and changes of frequency of abnormalities
- Central tendency analysis for absolute and changes from baseline in cardiac intervals
- Outlier analysis for absolute and changes from baseline in cardiac intervals.

In addition, the relationship between drug exposure and QT/QTc interval changes will be explored using scatter plots and regression analyses.

9.6.3.3 LVEF

LVEF will be summarized by treatment arm across time on study using descriptive statistics for actual values and for changes from baseline.

9.7 Pharmacokinetics

9.7.1 Demographics

Descriptive statistics of key demographic features of patients who completed the PK sub-study will be provided.

9.7.2 Pharmacokinetic parameters

The plasma concentrations will be used for non-compartmental pharmacokinetic evaluation with WinNonlin®. Calculated parameters will be reported with maximally 2 significant digits. Non-rounded values will be used for calculations. Therefore, minor variations in values may occur.

Descriptive statistics rather than inferential analyses will be provided, with tabulated and graphical displays of data and accompanying statistical commentary, where appropriate.

Where possible, the following parameters will be determined for each patient:

- AUC, area under the curve
- C_{max}, peak observed concentration
- T_{max}, time of peak concentration
- Apparent terminal elimination half-life
- Clearance
- Derived parameters for parent drug and metabolites

9.8 Population pharmacokinetics

Population pharmacokinetic methodology will be applied to analyze results derived from sparse PK sampling and from the PK sub-study. Details of the analyses to be performed will be specified in the Statistical Analysis Plan.

9.9 Interim analyses

The Data and Safety Monitoring Board (DSMB) will review data periodically throughout the trial. The DSMB may recommend stopping the trial for safety at any time or for futility at the interim looks. Two planned interim analyses will be conducted, one for futility only and one for both safety and efficacy. The first for a futility analysis only will be conducted at 1/3 of information time (i.e., approximately at 128 death event time). The interim efficacy/safety analysis is planned at 50 % of information time (when approximately 192 death events take place).

In the interim efficacy/safety analysis, OS, the primary efficacy outcome of the study, will be analyzed using a two-sided log-rank test. The Lan-DeMets implementation of the O'Brien Fleming boundary will be employed to control the overall non-binding Type I

error rate at 0.05. The nominal p-values for the planned second interim and the final analyses will be 0.003051 and 0.049002, respectively.

9.10 Power and sample size

Approximately 384 events of deaths will be required to achieve 80 % power to detect a treatment difference at the overall two-sided 0.05 significance level after taking the planned efficacy/safety interim look into account. It is expected that approximately 500 patients will be enrolled during an estimated 24-month recruitment period and will then be followed for 12 months to observe a total of approximately 384 death events. In the sample size calculation, it is assumed that the median OS is 12 months for the group with investigational treatment (AEZS-108) and 9 months for the control group (doxorubicin). The sample size calculation has taken the interim analyses into consideration.

10 ADMINISTRATIVE AND GCP ISSUES

The coordinating investigator has been informed in detail about the properties of the investigational drug. This included a review of the current version of the Investigator's Brochure (copy included in the Investigator's File). In multicenter trials, this information will also be made available to each locally responsible (principal) investigator.

10.1 Essential documents for trial initiation; Trial Master Files (TMF)

No study medication will be shipped to an investigational site before:

- the final protocol has been signed,
- the insurance for the participants has been issued, and
- the trial has been authorized by or notified to regulatory authority(ies) (where required),

and before the locally responsible (principal) investigator has provided to the sponsor the following “essential documents” (ICH-GCP):

- Written ethics committee (IEC/IRB) note on the review of the clinical trial protocol and informed consent form (and of other trial related documents as required locally)
- Signed *Agreement on Study Conduct* according to protocol (required for each center in a multicenter study)
- Signed *Financial Agreement* (between sponsor and each investigator/institution)
- List of *Authorized Study Personnel*
- Curriculum vitae of the principal investigator (updated, dated, and signed)
- Signed form pertinent to US 21 CFR 54 (Financial Disclosure; Form FDA 3455)
- Signed form pertinent to US 21 CFR 312 (Statement of Investigator; Form FDA 1572; mandatory for investigators in the US only)

Documents that the locally responsible investigator may provide to the sponsor at a later date, but not later than the first monitoring visit during the ongoing study:

- Curricula vitae of sub-investigators (updated, dated, and signed)
- Current laboratory normal ranges and documentation of laboratory certification (if applicable) (in multicenter trials required from each participating institution)

Both the sponsor and the investigator will maintain *Trial Master Files* (TMF) for the "essential documents" as specified by ICH-GCP. The sponsor will provide each principal investigator with a TMF, the *Investigator's File*, containing the relevant documents for the investigator's site. TMFs will be kept and updated by the sponsor and the investigator, respectively.

10.2 Subject information and consent

Based on the text of the subject (patient) information and consent form approved by the competent IEC/IRB, it is the investigator's obligation to:

- inform each subject accordingly and to allow sufficient time to decide whether or not to participate in the study;
- give patients, relatives or, if necessary, legal representatives the opportunity to enquire about details of the trial and to answer any questions regarding the study;
- ensure that the consent form has been signed and dated by her/himself and by the subject prior to study entry.

10.3 Protocol amendments

Any modification of the protocol has to be agreed upon between the coordinating investigator and sponsor in form of a written amendment and not implemented until signed by both parties. All protocol amendments should be forwarded to the EC/IRB. Amendments involving patients' safety, change in study design or a dose of study drug exceeding the dose-range planned in the escalation process) must be approved by each EC/IRB prior to implementation. Principal investigators from all participating institutions will have to acknowledge the receipt of the amendment.

10.4 Premature termination of the trial

The sponsor reserves the right to terminate the trial for well-documented reasons. Instructions will be provided if assessments beyond the regular per protocol procedures should be necessary. If the coordinating investigator concludes that termination of the trial may be required, he will immediately provide his evidence to the sponsor. An investigator, who wishes to discontinue his trial participation, will immediately inform the sponsor of his decision.

10.5 Documentation obligations

10.5.1 Data collection / electronic case report forms (eCRFs)

All trial data will be recorded on electronic CRFs (eCRF) supplied by the sponsor. Access to the eCRF will be restricted and password-controlled to the investigator and authorized co-workers according to the list of *Authorized Study Personnel.* Case report forms should be completed in English. Generic names for concomitant medications may be entered in the local language.

All data entries into eCRFs must be supported and verifiable from source documents to be retained in patient/hospital files.

Detailed guidance on the use of the eCRFs will be provided in a separate data entry training manual.

10.5.2 Confidentiality of data

Personal patient data will be kept confidential. CRFs or other documents submitted to the sponsor will identify a patient by initials and number only. Each investigator will keep in his file a *Screening/Enrolment Log + Patient Identification List* (including complete name and date of birth of each patient; original of the list in the investigator's file; on request, a copy without full names and address should be submitted to the sponsor). To allow compliance with GCP principles, each patient will be asked for consent regarding the access to source documents for monitoring, audits, and inspections. The agreement, covering also the use of the data for analysis has to be documented in writing, together with the written informed consent for trial participation.

10.6 Monitoring and inspections

10.6.1 Trial monitoring and data collection

The monitor and other nominated personnel of the sponsor will contact and visit the investigator's site regularly. The anticipated frequency is one visit or other contact every 6-8 weeks.

Amongst others, the following items will be reviewed:

- trial progress,
- compliance with the protocol,
- completion of CRFs,
- storage and accountability of trial drug,
- source data verification.

Monitoring visits will be recorded in a *Monitoring Log* at the investigator's site, and at the end of the trial, a copy of the completed form will be returned to the sponsor.

Source data verification (verification of data by comparing CRF entries with original laboratory reports and other patient records of the investigator): Data to be checked for each patient (100 % level) will include: patient identification, informed consent (procedure and dated signature), selection criteria, drug administration, adverse events, and primary efficacy parameter. Other efficacy and safety parameters will be checked at a 20 % level.

Any changes or corrections of CRF entries will be made by the investigator or by authorized study personnel. The investigator should retain records of the changes and corrections.

10.6.2 Data handling and processing

After receipt of CRFs, the monitor/clinical research associate will check these for completeness, legibility, and plausibility of the data. Additional checks will be performed

upon computerization (e.g. range checks, crosschecks). Where required, the investigator will be asked for supplemental information or CRF corrections.

10.6.3 Audits and inspections

Audits and inspections may be carried out by the sponsor's quality assurance department, local authorities, or authorities to whom information on this trial has been submitted. All documents pertinent to the trial must be made available for such inspection after an adequate announcement. Informed consent of patients participating in this study has to include the consent in this access to source documents. The anticipated frequency of audits and inspections done by the sponsor during the study will not exceed 2 visits for each study center.

10.7 Final report and publication

A report will be prepared under the responsibility and according to the standards of the sponsor. It will include the statistical analysis and raw data listings of efficacy and safety data. Safety data will also be summarized in the synopsis with special emphasis on suspected serious unexpected adverse drug reactions. It will be submitted to the coordinating investigator for acknowledgement and signature.

It is the policy of Aeterna Zentaris to encourage the presentation and publication of data resulting from clinical trials.

The following principles will be followed for the definition of authorship in multicenter trials:

- Authorship will include investigators who have recruited at least 10% of the total number of evaluable patients.
- The authors sequence should usually reflect the number of evaluable patients enrolled by the corresponding principal investigator.

The authorship will also include representatives of the sponsor.

Draft versions of abstracts or manuscripts must be made available to the co-authors and to the sponsor before any presentation of results or submission for publication. At least 3 weeks should be allowed for review and comment of an abstract and 4 weeks in case of a full paper, respectively. Multiple review cycles are usual for full papers and respective planning must account for this.

10.8 Archiving

The investigator must keep the following documents for at least 10 years beyond the end of the trial if the sponsor does not explicitly allow earlier disposal: patient identification codes, records of informed consent, IEC/IRB approval letter, dispensing logs, monitoring logs, CRF copies including copies of data clarification forms, correspondence, source documents including original reports of test results, and other “essential documents” (ICH- GCP) pertaining to the conduct of the trial. No document pertinent to the trial should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign these records to another party or move them to another location, written agreement must be obtained from the sponsor.

The sponsor will archive the originals of protocol, CRFs, and *Medication Accountability List*.

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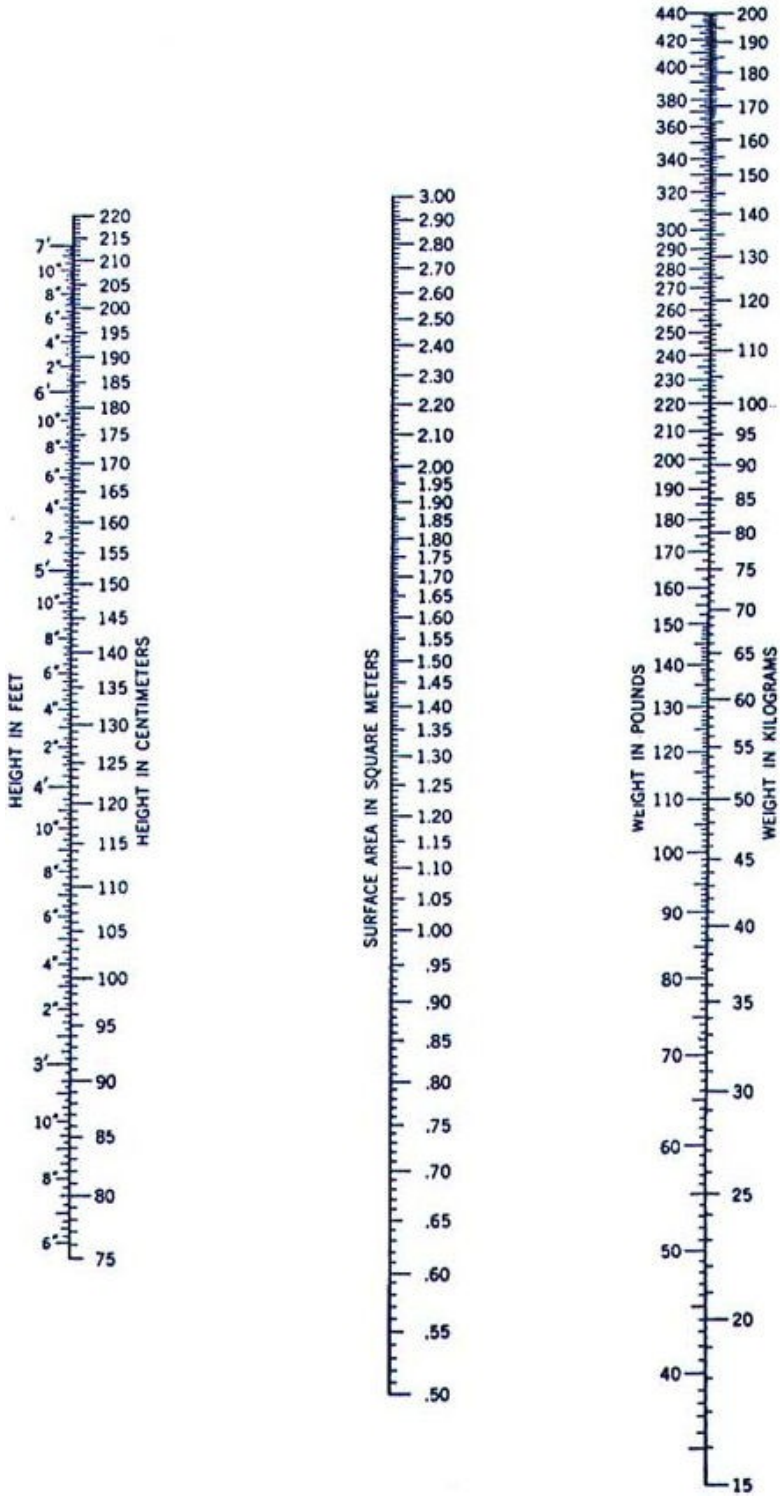
APPENDIX 1: CALCULATOR / NOMOGRAM FOR DETERMINATION OF BODY SURFACE AREA

For a BSA calculator, see: http://www.medcalc.com/body.html (use DuBois formula). For BSA and dose calculator, see: http://www.halls.md/body-surface-area/bsa.htm.
Source of the nomogram below: http://www.smm.org/heart/lessons/nomogram_adult.htm.



APPENDIX 2: ECOG PERFORMANCE STATUS SCALE

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50 % of the time. 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	In bed >50 % of the time. Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	100 % bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 3: GRADING OF LEFT VENTRICULAR FUNCTION (CTCAE-V4.03)

Adverse Event Category: Cardiac general

Adverse Event / Short Name: Left ventricular systolic dysfunction

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death

Adverse Event Category: Investigations

Adverse Event / Short Name: Ejection fraction (EF) decreased

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
-	Resting EF 50 – 40 %; 10 – 19 % drop from baseline	Resting EF 39 – 20 %; > 20 % drop from baseline	Resting EF < 20 %	Death

Source: CTCAE v4.03 publish date: June 14, 2010)

(see: *http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*)

APPENDIX 4: POTENTIALLY CARDIOTOXIC MEDICATION

Not applicable (this appendix was deleted per protocol amendment no. 3). Instead, please refer to protocol Section 6.3.2 (Prohibited therapy) and Section 6.3.3 (Interaction with other medicinal products and other forms of interaction).

APPENDIX 5: EXAMPLE OF GNRH AGONISTS AND ANTAGONISTS

Use of the following drugs is excluded within 6 months prior to study entry.

- **GNRH agonists:** triptorelin, buserelin, leuprorelin, goserelin
- **GNRH antagonists:** cetrorelix, ganirelix, degarelix, abarelix, ramorelix

APPENDIX 6: QUALITY OF LIFE QUESTIONNAIRES (SAMPLE SPECIMENS)

EORTC QLQ-C30 questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌊ ⌊ ⌊

Your birthdate (Day, Month, Year): ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊

Today's date (Day, Month, Year): 31 ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC Endometrial Cancer Module (QLQ-EN24)

ENGLISH

EORTC QLQ – EN24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had swelling in one or both legs?	1	2	3	4
32. Have you felt heaviness in one or both legs?	1	2	3	4
33. Have you had pain in your lower back and / or pelvis?	1	2	3	4
34. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
35. Have you passed urine frequently?	1	2	3	4
36. Have you had leaking of urine?	1	2	3	4
37. Have you had pain or a burning feeling when passing urine?	1	2	3	4
38. When you felt the urge to move your bowels, did you have to hurry to get to the toilet?	1	2	3	4
39. Have you had any leakage of stools?	1	2	3	4
40. Have you been troubled by passing wind?	1	2	3	4
41. Have you had cramps in your abdomen?	1	2	3	4
42. Have you had a bloated feeling in your abdomen?	1	2	3	4
43. Have you had tingling or numbness in your hands or feet?	1	2	3	4
44. Have you had aches or pains in your muscles or joints?	1	2	3	4
45. Have you lost hair?	1	2	3	4
46. Has food and drink tasted differently from usual?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at all	A little	Quite a bit	Very much
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you felt less feminine as a result of your disease or treatment?	1	2	3	4

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
49. To what extent were you interested in sex?	1	2	3	4
50. To what extent were you sexually active?	1	2	3	4
Answer these questions only if you have been sexually active during the past 4 weeks:				
51. Has your vagina felt dry during sexual activity?	1	2	3	4
52. Has your vagina felt short and / or tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

APPENDIX 7: PHARMACOKINETIC SUB-STUDY

1 BACKGROUND INFORMATION

1.1 Introductory Remarks

This Appendix provides details on the PK sub-study referred to in the clinical trial protocol AEZS-108-050 and described briefly in Section 7.3.3.

While targeted uptake of AEZS-108 by binding to LHRH receptors and internalization of bound AEZS-108 is the intended mode of action, circulating AEZS-108 also undergoes a hydrolytic cleavage releasing doxorubicin, the drug substance administered in the comparator arm. Therefore, the sub-study will also include patients treated with the comparator drug doxorubicin. In addition PK parameters of doxorubicinol, which is expected as the main metabolite of doxorubicin in both treatment arms, will be evaluated. Availability of PK data for all three analytes - AEZS-108, doxorubicin, and doxorubicinol - should help to better understand similarities and differences in therapeutic and safety results of the clinical study.

The PK-sub-study will be performed in selected sites of this multi-center and multi-national study. Only patients who take part in the main study will be eligible for inclusion in the sub-study. Sub-study specific procedures described here do not replace any of the procedures described for the main study.

1.2 Pharmacokinetics of AEZS-108

AEZS-108 (INN zoptarelin doxorubicin) is an LHRH-cytotoxic hybrid molecule. The cytotoxic molecule doxorubicin (DOX) is chemically linked to the carrier molecule D-Lys^6-LHRH (an LHRH agonist) which enables the specific binding and selective uptake of the hybrid molecule by tumors expressing receptors for LHRH ("drug targeting").

In non-clinical pharmacokinetic (PK) studies in rats and dogs, the $t_{1/2}$ (< 1 hr) and t_{max} (0.08 hr) of AEZS-108 and DOX were similar. Dose linearity for AEZS-108 was demonstrated when based on C_{max} and $AUC_{0\text{-}4h.}$ The AUCs of AEZS-108 were higher (3 to 9 times in rats, 7 to 12 times in dogs) than those of DOX after single and multiple doses, independent of dose and sex.

Only preliminary PK data from studies in human subjects are available. Following administration of 160 and 267 mg/m^2 AEZS-108 in a Phase I/II study [Emons et al., 2010], maximum plasma concentrations of 728 – 6661 ng/mL were measured. Because of the high variability, partly attributable to procedural deficiencies, neither a dose dependency of C_{max} values nor of the calculated AUC values could be shown. The calculated half life and the clearance of AEZS-108 were found to be in the range of 0.74 - 4.58 h and 0.37 - 2.67 l/min·m^2, respectively, and were independent of the dose level. This is an indication of dose linearity.

At the dose levels of 160 and 267 mg/m^2, the C_{max} values of the active metabolite doxorubicin were measured in the range of 177 – 1580 ng/mL. The ranges of half life and calculated clearance for doxorubicin, ranging 0.78 – 4.71 h and 0.33 – 1.43 l/min·m^2, respectively, were comparable to those for AEZS-108. The doxorubicin plasma concentrations and therefore the calculated AUC values of doxorubicin increased with increasing doses.

Recently, preliminary PK data have become available from an ongoing Phase I/II study in urothelial cancer (Study AEZS-108-046; unpublished data on file). In this study, sampling was scheduled 1 hour (h) after start of the infusion, within 10 minutes before end of the infusion (EOI), then 30 minutes, 1h, 2h, 3h, 4h, 6h, and 24h after EOI. Figure 1 shows the time courses of AEZS-108 and doxorubicin for 4 patients (3 males: #8, 10 and 11; 1 female: #9) who received AEZS-108 as a 2-hour infusion at the dose of 267 mg/m^2. In patient #8, the EOI sample was actually taken few minutes after EOI, thus explaining the higher concentration of doxorubicin in the sample taken 1h after the start of the infusion. In patient #11 (3-001), the EOI sample was hemolytic, thus possibly explaining the lower concentration of doxorubicin measured in this sample. Table 1 shows the ranges for C_{max} and AUC of AEZS-108 and doxorubicin concentrations for 4 patients after the AEZS-108 dose of 267 mg/m^2.

Table 1: Range of C_{max} and AUC values after AEZS-108 dose of 267 mg/m^2

[N=4]	**C_{max} [ng/mL]**	**AUC [ng x h/ mL**
AEZS-108	2862 - 5985	5704 – 12585
Doxorubicin	645* – 1814	3848 – 5501*

*hemolyzed sample

AEZS-108 is sensitive to spontaneous and/or carboxylesterase-catalyzed deconjugation into DOX and probably D-Lys^6-LHRH-glutarate in blood plasma and aqueous solutions. The rate of hydrolysis of AEZS-108 in mouse serum (approx. $t_{1/2}$ = 20 minutes) was significantly higher than in human serum (approx $t_{1/2}$ = 100 – 120 minutes). Investigations on the stability of AEZS-108 in microsomal liver incubations of both rat and man suggested a secondary role of metabolic decomposition compared with spontaneous hydrolysis.

The metabolism and excretion of doxorubicin that is hydrolytically released after intravenous administration of AEZS-108 is expected to be similar to the fate of intravenously administered doxorubicin [Speth et al., 1988].

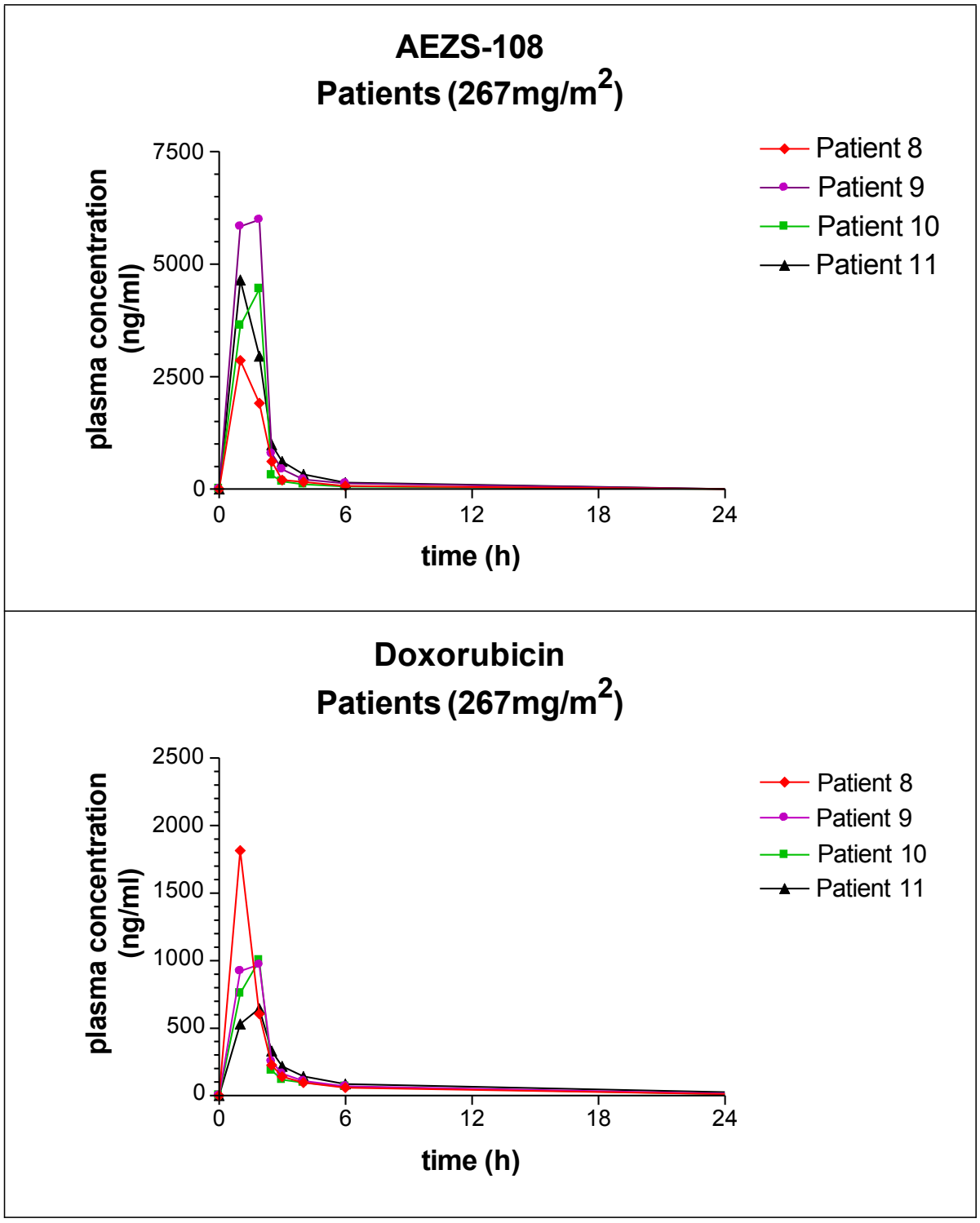


Figure 1: AEZS-108 and doxorubicin plasma concentration during and after a 2-hour intravenous infusion of AEZS-108 at 267 mg/m^2

1.3 Pharmacokinetics of doxorubicin

PK studies in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. The initial distribution half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 2 mM. Enzymatic reduction at the 7-position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol in patients is formation rate limited. The terminal half-life of doxorubicinol is similar to doxorubicin. The relative exposure of doxorubicinol, compared to doxorubicin ranges between 0.4 and 0.6. In urine, < 3% of the dose was recovered as doxorubicinol over 7 days. The literature contains no information regarding gender related differences in the pharmacokinetics of doxorubicin and doxorubicinol.

PK parameters for doxorubicin and doxorubicinol after a 1-hour infusion of doxorubicin have been reported from a study in patients with small cell lung cancer (SCLC) [Piscitelli et al., 1993], The study included 35 patients (24 males / 11 females) of which 4 subjects were classified as having impaired liver function defined as a GGT > 3 times normal and a bilirubin > 1.0 mg/dL. Doxorubicin at doses ranging of 45 to 72 mg/m^2 was administered in combination with cyclophosphamide (1000 mg/m^2) and vincristine (2 mg).

Figure 2 shows a scatter plot for the AUC of doxorubicin by dose of doxorubicin, and Table 2 summarizes the mean PK parameters for doxorubicin and doxorubicinol.

The patients with impaired liver function showed a significantly ($p < 0.05$) slower clearance (239 versus 666 ml/min/m^2), larger AUC (4610 versus 1834 ng • hr/mL) and longer elimination half-life (49.3 versus 25.6 hours) compared with patients with normal hepatic function.

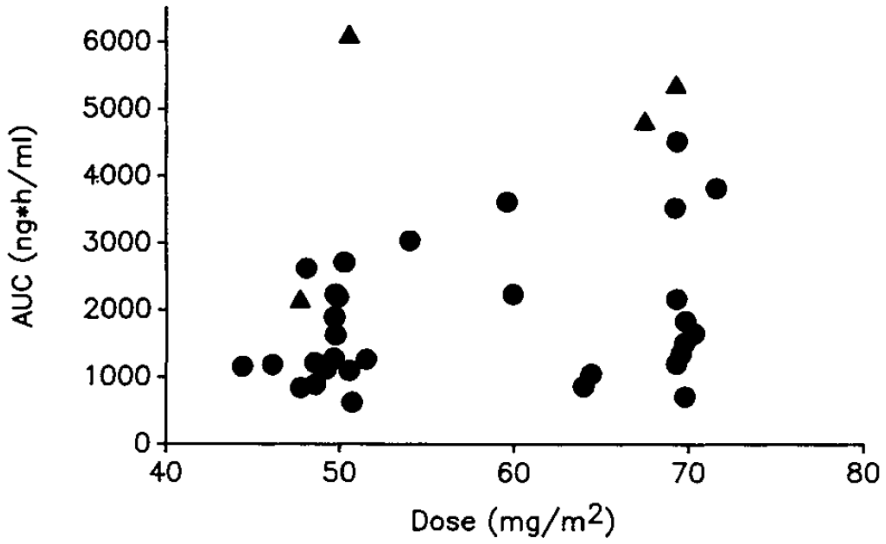


Figure 2: Doxorubicin dose and area under the concentration-time curve (AUC) in individual patients with *(triangles)* and without *(circles)* liver impairment

Table 2: Mean pharmacokinetic parameters of doxorubicin and doxorubicinol in patients with small cell lung cancer

	Normal	*Liver dysfunction*
Doxorubicin		
AUC (ng · hr/ml)	1834 ± 1007	4610 ± 1720*
CL (ml/min/m^2)	666.2 ± 339	238.8 ± 96*
$t_{1/2}$ (hr)	25.6 ± 16.9	49.3 ± 33.4*
V_C (L/m^2)	16.0 ± 17.2	9.40 ± 6.3
V_{SS} (L/m^2)	681.6 ± 433	578.5 ± 319
Doxorubicinol		
AUC (ng · hr/ml)	2529.7 ± 2699	3215.2 ± 1176
$t_{1/2}$ (hr)	29.1 ± 15.7	28.8 ± 16.7

Data are mean values ± SD.

AUC, Area under the concentration-time curve; CL, clearance; $t_{1/2}$, half-life; V_C, volume of distribution of central compartment; V_{SS}, volume of distribution at steady state.

*Statistically significant at $p < 0.05$.

1.4 Acute effects of doxorubicin on cardiac function

Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed

cardiotoxicity, are rarely of clinical importance, and are generally not considered an indication for the suspension of doxorubicin treatment.

Accordingly, a standard 12-lead ECG recording and 'rhythm strip' evaluation is considered sufficient for the monitoring of cardiac effects within this PK sub-study, which is limited to Cycle 1 dosing.

2 OBJECTIVES

To assess the pharmacokinetics of AEZS-108 after intravenous infusion over 2 hours.

To assess the exposure to AEZS-108's metabolites doxorubicin and doxorubicinol after a 2-hour intravenous infusion of AEZS-108 at 267 mg/m^2 in comparison to the exposure to doxorubicin and doxorubicinol after a short-term (1-hour) intravenous infusion of doxorubicin at 60 mg/m^2.

To assess the acute effects of intravenously administered AEZS-108 and doxorubicin on electrocardiographic parameters.

3 ETHICS

3.1 Benefit / risk considerations

The investigations planned in this sub-study are important for a better understanding of how AEZS-108 works, i.e., how the reversible chemical fixation of doxorubicin to an LHRH agonist affects the exposure of patients to doxorubicin and its main metabolite doxorubicinol.

It is not anticipated, however, that the results of this pharmacokinetic sub-study are immediately relevant for the assessment of the outcome or for the management of the study treatment in the individual patient.

Risks associated with blood sampling for PK analysis include local pain, hematoma, and infection. The risks are similar to the risks associated with blood sampling for routine safety tests.

3.2 Protection of patients

Before initiation of the sub-study, the corresponding protocol amendment of the study protocol will be reviewed by the competent independent ethics committees (IEC) for the study sites involved in the sub-study. The sub-study will be notified to the competent authorities.

The patients will be informed both verbally and in writing about the nature of this pharmacokinetic sub-study, the anticipated benefits and risks, the discomfort to which they may be exposed, and also their right to interrupt their participation at any time of their own free will. They will confirm their consent in writing prior to inclusion. The subject's informed consent form specific to this sub-study will be reviewed and approved by the IEC.

The Sponsor will insure adequate insurance coverage in the event of patient injury resulting from participation in this sub-study. Patients should be instructed to immediately notify the investigator of any injury that may have been caused by participation in this sub-study. A copy of the insurance conditions is included in the investigator's file.

4 STUDY DESIGN

Only selected study sites, which are equipped for and experienced in the sampling, processing, and storage of blood samples for drug concentration measurements will participate in this sub-study to Study AEZS-108-050.

It is planned that about 40 patients who have been randomly allocated to treatment with either AEZS-108 or doxorubicin (i.e., about 20 patients allocated to each treatment group) will take part in this PK sub-study.

Whereas the core protocol of the clinical study allows doxorubicin to be administered either as a bolus injection or a short term (up to 1 hr) infusion according to the study site's routine practice, the statistical evaluation of pharmacokinetic parameters requires the use of the same duration of infusion for all patients participating in the PK sub-study. The duration of the infusion of doxorubicin for the PK sub-study (Cycle 1) is being defined at 1 hour, which will allow mid- and end-of-infusion sampling in both the investigational and comparator group. Note: As the PK sampling is limited to Cycle 1, investigators will be free to use a different mode of administration (e.g., bolus injection) for subsequent treatment cycles for study participants, according to the institution's routine practice.

AEZS-108 and doxorubicin will be given as an intravenous infusion. If a peripheral vein is used for the infusion, the blood samples must be collected from a contralateral vein.

Pharmacokinetic investigations will be limited to Cycle 1, with blood sampling at pre-defined time points up to 72 hours after the start of the infusion. Samples will be analyzed for the plasma concentrations of AEZS-108, doxorubicin and doxorubicinol in the investigational arm (Arm A) and for doxorubicin and doxorubicinol in the comparator arm (Arm B).

Plasma concentrations of AEZS-108, doxorubicin, and doxorubicinol will be measured using validated methods.

The main PK parameters to be evaluated will include:

- AUC, area under the curve
- C_{max}, peak observed concentration
- T_{max}, time of peak concentration
- Apparent terminal elimination half-life
- Clearance
- Derived parameters for parent drug and metabolites

Further PK parameters may be calculated for each patient, where possible.

ECGs will be recorded before, during and after the end of the infusion as well as at the blood sampling time points around the expected T_{max} of the metabolites and 24 hours after end of the respective infusion. The ECGs will be evaluated for possible effects on the heart rate and electrocardiographic parameters.

4.1 Sample size and statistical considerations

This is an exploratory study in which the pharmacokinetics of the investigational drug AEZS-108 and the comparator drug doxorubicin will be evaluated for a descriptive analysis. Based on published data on the pharmacokinetics of doxorubicin, a sample size of 20 patients for each arm is proposed, to provide a more detailed description than is currently available for the key pharmacokinetic parameters of AEZS-108, doxorubicin, and doxorubicinol.

Based on preliminary pharmacokinetic data available from an ongoing study in bladder cancer patients, a variability of AEZS-108 similar to that for doxorubicin may be expected.

Since collection of only a limited number of samples ('sparse sampling') over a limited period (about 2-3 terminal elimination half-lives) is feasible within this sub-study, the comparison of the metabolite profiles will be orienting / exploratory / descriptive in nature.

5 PATIENT SELECTION

To be eligible for this sub-study, a patient must meet all of the eligibility criteria defined in the core protocol of Study AEZS-108-050. About 40 patients allocated to treatment with either AEZS-108 or doxorubicin will be asked to participate in this PK sub-study.

Because of the descriptive, exploratory nature of the analyses, patients who have been withdrawn or who dropped out before completion of the PK blood sampling will not be replaced. Since the blood samples will be collected only over a short period, a high rate of early discontinuations from sub-study procedures is not anticipated.

6 BLOOD SAMPLING AND PROCESSING AT STUDY SITES

6.1 Time schedule of blood sampling (and ECG monitoring)

The following table indicates the targeted time for blood sampling, the window for acceptable deviations from the targeted sampling time and the reference point for the window in relation to the start or end time of the infusion.

With regard to the shorter infusion duration for doxorubicin, the sampling schedule for the post-infusion samples for both treatment groups is defined in relation to the end-of-infusion (EOI), as shown in Table 3. At the indicated time points, ECGs will be recorded within a time window of 10 minutes prior to the corresponding blood collection times.

Table 3: Schedule for blood sampling and ECG recording

#	**Time relative to infusion**	**Sampling time window**	**12-lead ECG** (up to 10 minutes before blood sampling)
1	Pre-Dose	Up to 30 minutes **before the start of the infusion**	ECG #1
2	Mid of infusion [a)]	After the start of the infusion: AEZS-108: 60 +/- 2 minutes Doxorubicin: 30 +/- 2 minutes	ECG #2
3	**End of Infusion (EOI)** [a)]	Up to 5 minutes **before EOI**	ECG #3
4	30 minutes **after EOI** [b)]	+/- 2 minutes	ECG #4
5	1 hour **after EOI** [b)]	+/- 2 minutes	ECG #5
6	2 hours **after EOI** [b)]	+/- 2 minutes	ECG #6
7	4 hours **after EOI** [b)]	+/- 2 minutes	*(no ECG)*
8	6 hours **after EOI** [b)]	+/- 2 minutes	*(no ECG)*
9	24 hours **after EOI** [b)]	+/- 2 hours	ECG #7
10	48 hours **after EOI** [b)]	+/- 4 hours	*(no ECG)*
11	72 hours **after EOI** [b)]	+/- 4 hours	*(no ECG)*

a) Scheduled duration/end of infusion is 2 hours for AEZS-108 and 1 hour for doxorubicin; an infusion pump should be used to ensure the desired rate and duration of the infusion;
b) EOI (end of infusion); all subsequent sampling times refer to the **actual** end of infusion

A 2-minute window is acceptable for all time points on Day 1, except for the end of infusion (EOI) sample which must NOT be taken after the end of infusion. Therefore sampling up to 5 minutes **before** the end of infusion is acceptable for the EOI sample. The actual time of the EOI must be recorded and will direct the timing of post-EOI sampling times.

While the targeted duration of the infusion is 2 hours for AEZS-108 and 1 hour for doxorubicin, the actual duration of the infusion may vary slightly. As the plasma concentration of the infused drug will rapidly decrease after EOI due to tissue distribution, the EOI sample must be taken shortly before (!) the EOI has been reached, in order to reliably determine the maximum plasma concentration (C_{max}). For the timing of the post-EOI samples, it is important to determine the actual EOI, so that the distribution of the administered drug, in the case of AEZS-108 the hydrolytic release of doxorubicin, can be evaluated reliably.

The time when the blood sampling actually occurred (hh:mm) has to be documented in the respective source document and CRF. Deviations outside these time limits must be commented upon.

6.2 Blood sampling and processing

Blood samples (5.4 mL) will be collected into appropriately labeled potassium ethylenediamine tetraacetate (K-EDTA) tubes (purple top) at the times indicated. The specimen will be completely and gently inverted at least 10 times (and kept on ice prior to centrifugation) followed by centrifugation in a refrigerated centrifuge (2-8°C) at 1500g for 10 minutes. The plasma must be transferred into cryovials (200 µL/vial).

The labels of the cryovials have to provide at least the following:

- Study ID: AEZS-108-050
- Site code
- Subject ID number
- Scheduled sampling time (as named as in the column named 'Scheduled time of blood sampling and ECG recording' in Table 3).

The actual sampling time (in the format hh:mm, using 24 hour clock) will be provided by the site in a sampling record, to enable calculation of any deviations from the scheduled sampling time.

6.3 Storage and shipment of frozen plasma samples

Within 30 minutes of the sampling time, the cryovials must be stored at -20 °C.

Storage at -20 °C should not exceed a period of 3 months. Unless a subsequent study patient is expected to enter the PK sub-study within the next month, shipments to the bioanalytical facility should be arranged within 1 month after collection, so that samples can be analyzed within 3 months from collection, possibly together with samples received from other sites participating in this sub-study.

One set of the split samples for a given sampling series will be sent to the bioanalytical facility, together with a copy of the sampling records. The second set of the split samples will be retained as reserve, in case of problems with the shipment of the first set.

Shipment address:

Prolytic GmbH
c/o. Dr. Dorothee Krone
Alt Fechenheim 34
D-60386 Frankfurt am Main, Germany
Tel.: +49 69 4109 2535
Fax: +49 69 4269 4784
e-Mail: dorothee.krone@prolytic.de

7 BIOANALYTICAL PROCEDURES

Concentrations of AEZS-108, doxorubicin, and doxorubicinol in human plasma samples will be analyzed by validated methods. The processing of the plasma samples is based on a liquid/liquid phase extraction. For undiluted test samples, the lower limits of quantification (LLOQ) of the methods are about 5 ng/mL for all analytes.

All plasma test samples will be stored at approx. –20 °C after arrival at the test facility. Stability of analytes during storage at -20°C and after repeated freeze/thaw cycles has been shown [Ref. 4].

Calibration standards prepared by spiking human blank plasma with each analyte will be used for each analytical run. Quality control (QC) samples will be analyzed together with each batch of test samples. QC samples, containing each analyte at three concentration levels (low, medium, high) will be spiked by an independent person. Calibration curves will be established based on the calibration standard results for each analyte. The HPLC software will be used to calculate the concentrations of the test and QC samples on the basis of the corresponding calibration curve.

The acceptance criteria for the calibration standards in analytical batches can be summarized as follows: 75 % of the total number of standards, or a minimum of six standards, should be accepted, if the back-calculated value is within ± 15 % of the nominal value (except for the lowest concentration calibration standard, where the criterion is ± 20 % of the nominal value). Acceptance criteria for the quality control samples in analytical batches are defined accordingly: If more than one third of the QC samples or all QC samples of the same concentration level differ by more than ± 15 % from the theoretical values, the analytical series will not be accepted and the relevant test samples will be re-analyzed.

8 ECG MONITORING

Prior to collection of the PK blood samples #1 (predose) through #6 (2 hours after EOI), and prior to collection of the PK blood sample #7 (24 hours after EOI), triplicate standard 12-lead ECG will be recorded using the ECG equipment at the site. For immediate safety assessment the investigator will evaluate each ECG record for abnormalities or changes of ECG parameters. The results of the ECG evaluation will be recorded in the eCRF module for the PK sub-study.

In addition all changes in the ECG that are considered ‘clinically relevant’ will be recorded in the Adverse Events section of the eCRF for the core study.

All recorded paper ECG printouts will also be sent to an ECG core laboratory for central evaluation. Therefore, the original paper ECGs will be collected by the ECG core lab while hardcopies will be retained at the study site.

At the core lab the ECGs will be evaluated by a board certified cardiologist with particular emphasis on T and U wave morphology. In addition the core lab will measure the intervals RR, PQ (PR), QRS, and QT interval from the digitized wave forms using the core lab’s validated procedures and programs.

From the RR and QT intervals the heart rate and the heart rate corrected QTc interval will be calculated according to Bazett's and Fridericia's formula.

The resulting categorical and continuous variables will be analyzed statistically for possible influences of the study drugs on cardiac safety parameters.

9 REFERENCES

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2. Speth PA, van Hoesel QG, Haanen C. Clinical pharmacokinetics of doxorubicin. Clin Pharmacokinet. 1988 Jul;15(1):15-31. Review.
3. Piscitelli SC, Rodvold KA, Rushing DA, Tewksbury DA. Pharmacokinetics and pharmacodynamics of doxorubicin in patients with small cell lung cancer. Clin Pharmacol Ther. 1993 May;53(5):555-61.