Clinical trial results:
Randomised controlled study comparing AEZS-108 with doxorubicin as second line therapy for locally advanced, recurrent or metastatic endometrial cancer (ZoptEC study)

Summary

EudraCT number	2012-005546-38
Trial protocol	CZ BE GB AT DE ES IE IT BG NL PL DK FI
Global end of trial date	02 February 2017

Results information

Result version number	v1 (current)
This version publication date	11 February 2018
First version publication date	11 February 2018

Trial information

Trial identification

Sponsor protocol code	AEZS-108-050

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01767155
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aeterna Zentaris GmbH
Sponsor organisation address	Weismuellerstr. 50, Frankfurt am Main, Germany, 60314
Public contact	Clinical trial information desk, Aeterna Zentaris GmbH, +49 69426023429, clinical.trials@aezsinc.com
Scientific contact	Clinical trial information desk, Aeterna Zentaris GmbH, +49 69426023429, clinical.trials@aezsinc.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2017
Global end of trial reached?	Yes
Global end of trial date	02 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

On a regular basis, results from safety analyses were submitted to an independent Data and Safety Monitoring Board (DSMB) that advised the Sponsor of potentially critical findings.
Safety evaluation comprised collection of data related to adverse events, clinical laboratoy parameters, ECGs and data on left ventricular ejection fraction (LVEF).

Background therapy:

No specific background therapy was defined for this trial.
One of the eligibilty criteria for this trial was: "No. 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."
Relevant exclusion criteria in this context:
"No. 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.
No 8: Previous anthracycline-based chemotherapy (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone and valrubicin), in any formulation.
No 9: Anticipated ongoing concomitant anticancer therapy during the study."
All concomitant medications and therapies had to be recorded in the case report form.
Permitted therapies defined in the protocol included antiemetics, anti-allergic treatments, hematopoietic blood components in case of delayed hematological recovery, colony stimulation factors, as well as supportive and palliative treatment without any anticancer effect.
Prohibited therapies included concomitant anticancer therapies, live vaccines, amiodarone, and sotalol.

Evidence for comparator:

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 %), but also in patients without prior chemotherapy (11.5%), which could have been due to the selection of patients with less favorable prognosis for the latter trial.
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 was excluded.

Actual start date of recruitment	31 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	26 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Bosnia and Herzegovina: 6
Country: Number of subjects enrolled	Belarus: 9
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 43
Country: Number of subjects enrolled	Ukraine: 31
Country: Number of subjects enrolled	United States: 140
Worldwide total number of subjects	511
EEA total number of subjects	218

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	266
From 65 to 84 years	245
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The 511 patients who received treatment were enrolled in a total of 112 study centers in Europe, North America, and Israel.

Pre-assignment

Screening details:

Overall, 592 patients were screened and, of these, 81 patients failed the screening criteria and did not receive treatment with study medication.

Pre-assignment period milestones

Number of subjects started	511
Number of subjects completed	511

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AEZS-108 / Zoptarelin Doxorubicin

Arm description:

- Experimental: AEZS-108 / zoptarelin doxorubicin
- 267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles
- up to 9 cycles

Arm type	Experimental
Investigational medicinal product name	Zoptarelin doxorubicin
Investigational medicinal product code	AEZS-108
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles for a maximum of 9 cycles

Arm title	Doxorubicin

Arm description:

Active Comparator, standard chemotherapy
60 mg/m^2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg/m^2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles

Number of subjects in period 1	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin
Started	256	255
Modified Intention to Treat (mITT)	252	249
Safety Population (SAF)	252	249
Completed	243	240
Not completed	13	15
Protocol deviation	13	15

Baseline characteristics

Reporting groups	
Reporting group title	AEZS-108 / Zoptarelin Doxorubicin
Reporting group description:	
- Experimental: AEZS-108 / zoptarelin doxorubicin - 267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles - up to 9 cycles	
Reporting group title	Doxorubicin
Reporting group description:	
Active Comparator, standard chemotherapy 60 mg/m^2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles	

Reporting group values	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin	Total
Number of subjects	256	255	511
Age categorical Units: Subjects			
Adults (18-64 years)	130	136	266
From 65-84 years	126	119	245
Age continuous Units: years			
arithmetic mean	63.7	63.8	
standard deviation	± 8.63	± 8.81	-
Gender categorical Units: Subjects			
Female	256	255	511
Male	0	0	0
ECOG PS			
Eastern Cooperation Oncology Group Performance Status			
Units: Subjects			
Grade 0	120	125	245
Grade 1	121	118	239
Grade 2	15	11	26
Grade unknown	0	1	1
Stage of endometrial cancer at study entry			
Advanced disease stage comprising FIGO (The International Federation of Gynecology and Obstetrics) III or IV			
Units: Subjects			
Advanced (FIGO III or IV)	99	94	193
Metastatic	86	90	176
Recurrent	71	71	142

Subject analysis sets	
Subject analysis set title	Intention-to-treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population included all randomized patients. Analyses of this population assigned patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Reporting group values	Intention-to-treat (ITT)		
Number of subjects	511		
Age categorical Units: Subjects			
Adults (18-64 years)	266		
From 65-84 years	245		
Age continuous Units: years			
arithmetic mean	63.7		
standard deviation	± 8.71		
Gender categorical Units: Subjects			
Female	511		
Male	0		
ECOG PS			
Eastern Cooperation Oncology Group Performance Status			
Units: Subjects			
Grade 0	245		
Grade 1	239		
Grade 2	26		
Grade unknown	1		
Stage of endometrial cancer at study entry			
Advanced disease stage comprising FIGO (The International Federation of Gynecology and Obstetrics) III or IV			
Units: Subjects			
Advanced (FIGO III or IV)	193		
Metastatic	176		
Recurrent	142		

End points

End points reporting groups

Reporting group title	AEZS-108 / Zoptarelin Doxorubicin

Reporting group description:

- Experimental: AEZS-108 / zoptarelin doxorubicin
- 267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles
- up to 9 cycles

Reporting group title	Doxorubicin

Reporting group description:

Active Comparator, standard chemotherapy
60 mg/m^2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles

Subject analysis set title	Intention-to-treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population included all randomized patients. Analyses of this population assigned patients the treatment they were scheduled to receive, regardless of any errors of dosing or dose modifications.

Primary: Compare the Overall Survival (OS) of Patients Treated With AEZS-108 to the OS of Patients Treated With Doxorubicin

End point title	Compare the Overall Survival (OS) of Patients Treated With AEZS-108 to the OS of Patients Treated With Doxorubicin

End point description:

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

The final analysis, which was event-based, was conducted after approximately 384 randomized patients had died.

A log-rank test with an overall two sided Type I Error rate of 0.05 after taking the interim analyses into account was used to compare OS between the two treatment arms via a SAS LIFETEST procedure.

End point type	Primary

End point timeframe:

3 years

End point values	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	255		
Units: Events				
Survival Events	196	188		
Censored	60	67		
Survivors at 6 months	171	174		
Survivors at 12 months	111	106		

Statistical analyses

Statistical analysis title	Hazard ratio

Statistical analysis description:

A Cox model with treatment effects was used to estimate the hazard ratio and perform hypothesis testing. The estimated hazard ratio and the 95% CI of the hazard ratio were presented.

Comparison groups	AEZS-108 / Zoptarelin Doxorubicin v Doxorubicin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5441
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.3

Secondary: Compare Efficacy Based on Objective Response Rate (ORR)

End point title	Compare Efficacy Based on Objective Response Rate (ORR)

End point description:

The ORR was defined as the sum of the Complete Response (CR) and Partial Response (PR).
CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) was to have a reduction in the short axis to <10 mm.
PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
All responses were confirmed at least 4 weeks after the initial response was observed. Tumor assessments occurred every 3 cycles (± 7 days) during ongoing treatment then every 3 months (± 7 days) thereafter while the patient was on study.
The last assessment occurred either when progression was confirmed or when approximately 384 randomized patients had died.

End point type	Secondary

End point timeframe:

3 years

End point values	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	255		
Units: Subjects				
Complete Response (CR)	6	5		
Partial Response (PR)	26	31		
Objective Response Rate (ORR)	32	36		

Statistical analyses

Statistical analysis title	Compare Efficacy based on ORR

Statistical analysis description:

Hypothesis testing between the two treatment arms was performed using a Mantel Haenszel test. The odds ratio and 95% CI of the odds ratio were presented.

Comparison groups	AEZS-108 / Zoptarelin Doxorubicin v Doxorubicin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5907
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.45

Secondary: Compare Efficacy Based on Progression-free Survival (PFS)

End point title	Compare Efficacy Based on Progression-free Survival (PFS)

End point description:

Progression-free survival (PFS) was defined as the days between randomization and the date of documented progression or death for any cause. For patients whose progression status could not be determined, their PFS data was censored for the last adequate progression assessment date that the patient was confirmed to have no progression.

End point type	Secondary

End point timeframe:

3 years

End point values	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	255		
Units: Subjects				
PFS events	166	148		
Censored	90	107		
Survivors at 6 months	69	51		
Survivors at 12 months	28	12		

Statistical analyses

Statistical analysis title	Compare Efficacy based on PFS

Statistical analysis description:	
Hypothesis testing between the two treatment arms was performed using a log rank test.	
Comparison groups	AEZS-108 / Zoptarelin Doxorubicin v Doxorubicin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3089
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.11

Secondary: Compare Efficacy Based on Clinical Benefit Rate (CBR)

End point title	Compare Efficacy Based on Clinical Benefit Rate (CBR)
End point description:	
Clinical benefit was defined as having stable disease (SD) or better lasting for at least 9 weeks. The CBR was analyzed using the same methods for the ORR analyses. The analysis of CBR (CR+PR+SD) was performed in the ITT population. CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) was to have a reduction in the short axis to <10 mm. PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.	
End point type	Secondary
End point timeframe:	
3 years	

End point values	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	255		
Units: Subjects				
CR	6	5		
PR	26	31		
SD	106	102		
Progressive Disease (PD)	65	67		

Statistical analyses

Statistical analysis title	Compare Efficacy based on CBR
Statistical analysis description:	
Hypothesis testing between the two treatment arms was performed using a Mantel Haenszel test.	

Comparison groups	AEZS-108 / Zoptarelin Doxorubicin v Doxorubicin
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6924 [1]
Method	Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.52

Notes:

[1] - 2-sided test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall ca. 3 years. SAEs occurring or observed from the day of first administration of the investigational drug on and until 4 weeks after last administration (development of imparied cardiac function within 1 year after last IMP).

Adverse event reporting additional description:

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 4.03 or subsequent ones) were to be used for the grading of severity of symptoms and abnormal findings.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	AEZS-108 / Zoptarelin Doxorubicin

Reporting group description:

- 267 mg/m^2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles up to 9 cycles
- AEZS-108 / zoptarelin doxorubicin: 267 mg/m2 by 2-hour intravenous infusion, on Day 1 of 21-day (3-week)
- cycles for a maximum of 9 cycles

Reporting group title	Doxorubicin

Reporting group description:

- 60 mg/m^2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles
- doxorubicin: 60 mg/m2 by intravenous bolus injection or 1-hour intravenous infusion, on Day 1 of 21-day (3-week) cycles

Serious adverse events	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 252 (36.51%)	75 / 249 (30.12%)	
number of deaths (all causes)	196	188	
number of deaths resulting from adverse events	3	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	21 / 252 (8.33%)	15 / 249 (6.02%)	
occurrences causally related to treatment / all	21 / 21	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	17 / 252 (6.75%)	8 / 249 (3.21%)	
occurrences causally related to treatment / all	17 / 17	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anemia			
subjects affected / exposed	16 / 252 (6.35%)	9 / 249 (3.61%)	
occurrences causally related to treatment / all	15 / 16	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	8 / 252 (3.17%)	3 / 249 (1.20%)	
occurrences causally related to treatment / all	8 / 8	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 252 (0.40%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 252 (4.37%)	8 / 249 (3.21%)	
occurrences causally related to treatment / all	6 / 11	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	5 / 252 (1.98%)	3 / 249 (1.20%)	
occurrences causally related to treatment / all	3 / 5	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 252 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AEZS-108 / Zoptarelin Doxorubicin	Doxorubicin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	245 / 252 (97.22%)	245 / 249 (98.39%)	

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	134 / 252 (53.17%)	128 / 249 (51.41%)	
occurrences (all)	134	128	
Anemia			
subjects affected / exposed	121 / 252 (48.02%)	111 / 249 (44.58%)	
occurrences (all)	121	111	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	135 / 252 (53.57%)	143 / 249 (57.43%)	
occurrences (all)	135	143	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2013	Further clarifications on Inclusion criterion #5 and Exclusion criterion #6, #7, #8, #14, and #19. Clarification of timing of cardiac function tests. Clarification of drug reconstitution instructions and dosing calculations. Modification of SAE reporting. Allowed lifetime dose for doxorubicin increased.
12 September 2014	Addition of global and sparse PK assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported