2 SYNOPSIS

Title of Study:

Antitumoral activity and safety of AEZS-108 (AN-152), a LHRH agonist linked doxorubicin, in women with LHRH receptor positive gynecological tumors.

Note: The following synopsis pertains to endometrial cancer patients (Stratum B of the study). Stratum A of the study (ovarian cancer patients) is presented in report AEZS-108-040(OC)_01.

Investigators:

Principal investigator: Prof. Dr. med. Günter Emons, Göttingen, Germany (236)

Investigators: Dr. med. Anne Stähle, Karlsruhe, Germany (011)

Prof. Dr. med. Matthias Beckmann, Erlangen, Germany (045)

Dr. med. Lars Hanker, Frankfurt, Germany (151)

Prof. Dr. med. Jalid Sehouli, Berlin, Germany (201)

Dr. med. Philipp Harter (then: Dr. med. Rita Hils), Wiesbaden, Germany (239)

Dr. med. Pauline Wimberger, Essen, Germany (283)

Prof. Dr. Grigor Gortchev, Pleven, Bulgaria (500)

Dr. Violina Taskova, Varna, Bulgaria (501)

Dr. Arman Hristamjan, Plovdiv, Bulgaria (502)

Study centers:

011: St. Vincentius Kliniken AG Frauenklinik, Edgar-von-Gierke Str. 2, Karlsruhe, Germany

045: Universität Erlangen-Nürnberg, Klinik für Frauenheilkunde, Universitätsstr. 21-23, Erlangen, Germany

151: Klinikum der JWG Universität Frankfurt, Universitätsfrauenklinik, Theodor-Stern-Kai 8, Frankfurt, Germany

201: Charité Campus Virchow-Klinikum, Klinik für Frauenheilkunde und Geburtshilfe, Berlin, Germany

236: Georg-August-Universität Göttingen, Frauenklinik, Göttingen, Germany

239: Dr. Horst Schmidt Kliniken GmbH, Klinik f. Gynäkologie u. Gyn. Onkologie, Ludwig-Erhard-Str. 100, Wiesbaden, Germany

283: Universitätsklinikum, Universitätsfrauenklinik, Hufelandstr. 55, Essen, Germany

500: University Hospital “Dr. Georgy Stranski”, 20 “Sv. Sv. Kitil I Metodii” str., 5800, Pleven, Bulgaria

501: Regional Oncodispensary “M.Markov”, 100 Tsar Osvoboditel Blvd, 9010, Varna, Bulgaria

502: Regional Oncodispensary, II. Department of Internal Diseases, 2A, “A. Stamboliiski” Blvd., 4002, Plovdiv, Bulgaria

Publication (reference):

Emons G, Sehouli J, Gorchev G, Stähle A, Hanker L, Wimberger P, Beckmann M, Taskova V, Gruendker C
Phase II study AEZS-108, a targeted cytotoxic LHRH analog, in patients with LHRH

receptor positive endometrial cancer. Protocol AGO-GYN 5, AGO Study Group, Germany
November 2010 ENA Meeting Proceedings: Abstract 378

Study period:	**Phase of development:**
First patient enrolled: 02-Apr-2008 Last patient completed: 19-Sep-2011	II

Objectives:

- To evaluate the efficacy of the study treatment by assessing the partial or complete response rate according to RECIST and/or GCIG guidelines
- To evaluate time to progression (TTP) and overall survival (OS)
- To characterize the profile of adverse reactions, including remarkable changes of laboratory parameters

Methodology:

Open-label, non-comparative multicenter trial, stratified two-stage Simon design.

Number of patients (planned/analyzed):

Stratum B (endometrial cancer): Step 1: 21 / 21
Step 2 (if ≥ 2 responders in step 1): 20 / 22

Diagnosis and main criteria for inclusion:

- Women ≥ 18 years of age
- LHRH receptor positive tumor status from primary tumor

Stratum B - endometrium cancer:

- Histologically confirmed endometrial cancer
- Advanced (FIGO III or IV) or recurrent disease not amenable to potentially curative treatment with local surgery and/or radiation therapy
- No previous anthracycline-based chemotherapy
- Previous endocrine therapy is allowed
- At least one measurable target lesion according to RECIST criteria

Test product, dose and mode of administration, batch number:

AEZS-108 was administered intravenously at a dose of 267 mg/m^2 every Day 1 of a 21-day (3-week) cycle.

Dose reduction to 160 mg/m^2 when dose-limiting drug-related AEs occurred.

Recommended prophylactic anti-emetic: 8 mg dexamethasone

Batch number: P03807, P08706, P05907

Duration of treatment: planned maximum of six cycles (allowing on a case by case up to eight cycles based on tumor response and tolerability)

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Criteria for efficacy evaluation:

Tumor response per RECIST 1.0, TTP and OS.

Criteria for safety evaluation:

Adverse Events, (per CTCAE), clinical laboratory, vital signs, left ventricular ejection fraction (LVEF) and electrocardiogram (ECG)

Statistical Methods:

Kaplan-Meier analysis for TTP and OS. Frequency tables and descriptive statistics for safety parameters.

Summary:

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 %).

Efficacy results:

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 1).

Table 1: Best overall response

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 following patients: 101057, 201030 and 502300.

[b]: Patient 236052: The investigator reported SD at cycle 1 in the CRF. However this tumor assessment had not been completed post-treatment since it occurred on day 1 of cycle 1. Thus for reporting purposes, 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: patient 101017 and 201047

[d]: Non-cancer death prior to cycle 2: patient 500120

[e]: Tumor assessments not evaluable per reviewer: patient 011055, 201028 and 502301.

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.

Safety results:

Twenty-eight 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 %).

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) led to AEZS-108 discontinuation.

The most frequent grade ≥ 3 hematological abnormalities were leukopenia, neutropenia and lymphocytopenia.

Leukopenia of grade ≥ 3 was observed in roughly 13 % to 26 % of the patients, at each cycle and only on Day 15.

Neutropenia of grade ≥ 3 was observed in roughly 32 % to 54 % of the patients, at each cycle and only on Day 15.

Lymphocytopenia of grade ≥ 3 was observed in roughly 6 % to 20 % of the patients at each cycle on Day 8 and in some cases on Day 15 and 22.

No laboratory abnormalities led to study drug discontinuation.

No cardiac toxicity was reported based on LVEF.

Conclusion:

AEZS-108 given as a 2-hour IV infusion at 267 mg/m^2 every 3 weeks was active in 43 advanced or recurrent endometrial cancer patients with LHRH receptor positive tumor status, based on a 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. AEZS-108 was well tolerated in these patients: 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 hematotoxicities were leukopenia, neutropenia (both occurring only on Day 15 of each cycle) and lymphocytopenia (observed on Day 8, and in some cases on Day 15 and 22 of each cycle). These 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.

Date of the report: 23 July 2012