CLINICAL STUDY PROTOCOL PROC0319

OPEN-LABEL RANDOMIZED CLINICAL TRIAL OF EFFICACY AND SAFETY OF ELENAGEN VACCINE IN COMBINATION WITH GEMCITABINE IN PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

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NCT number **NCT05979298**

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This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

PROTOCOL SYNOPSIS

Title	OPEN-LABEL RANDOMIZED CLINICAL TRIAL OF EFFICACY AND SAFETY OF ELENAGEN VACCINE IN COMBINATION WITH GEMCITABINE IN PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER
Background/rational	This study is part of the contract between "CureLab Oncology, Inc."and N. N. Alexandrov RNPC from 3.18.2019
The purpose of the study	***Primary outcome :*** Progression-free survival (PFS) ***The main secondary objectives:*** •Safety and tolerability ***Other secondary objectives:*** • Overall response rate (ORR) • Disease control rate (DCR)
The planned sample size	40 patients (20 patients of the main group and 20 patients of the control group).
Study design	This is a randomized study conducted on parallel groups of patients. Patients meeting the eligibility criteria will be centrally randomized (1:1) in the control group (chemotherapy) and the main group (the same chemotherapy + ELENAGEN)
Duration of treatment	The use of ELENAGE continues regardless of disease progression, until intolerable toxicity or patient's refusal from the further use of the drug. Initially applied chemotherapeutic scheme can be changed at the discretion of the physician (one or more times) without stopping the use of ELENAGEN.
Primary and secondary endpoints	As the primary endpoint of the study it will be considered: the time to the progression of the tumor and/or the transition of the tumor process from the non-resectable to the resectable state. As secondary points of the study it will be considered: - Immediate effectiveness of treatment in accordance with the criteria of RECIST 1.1. - Overall survival. - The nature, frequency and severity of adverse reactions (CTCAE NCI, revision 5).

Statistical methods	**Criterion for evaluating the effectiveness of overall survival (OS)** OS is defined as the length of time from the date of randomization to the date of death. If no fatal outcome is recorded during the study, the time period will be limited to the last day on which the patient was known to be alive, or the date on which clinical data collection is completed, whichever comes first. As part of the analysis of the primary final evaluation OS criterion, the comparison of the two treatment groups will be carried out using a stratified logarithmic rank criterion using 3 stratification factors in randomization according to the treatment prescribed by the randomization system. The risk ratio (RR) with the corresponding 2-sided 95% confidence intervals (CI) will be assessed using the stratified Cox proportional hazards model (CPH). Survival for each group will be presented using Kaplan-Meier curves, followed by a description in terms of median and probability of survival in 3, 6, 9 and 12 months, with corresponding 2-sided 95% CI for these estimates. **The criterion for evaluating the effectiveness of progression-free survival (PFS).** The assessment of PFS will be performed from the date of randomization to the first registration of disease progression based on the results of CT examination or death. For the comparison of treatment groups in relation to the PFS the same analytical methods will be applied as in the valuation according to the final criterion of OS. Other secondary end criteria of effectiveness evaluation A comparison of the overall response rate (ORR) and the disease control rate (DCR) between treatment groups will be made using Fisher's exact test with the corresponding 95% CI. Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Two-sided, 95% confidence intervals will be calculated as appropriate. By-subject listings of data for all completed and discontinued subjects will be provided.

1. INTRODUCTION

1.1. Platinum-Resistant Ovarian Cancer

"Platinum resistant" ovarian cancer was historically defined as disease recurrence within 6 months of completion of first-line platinum-based chemotherapy, although this is now more broadly applied to also include patients progressing within 6 months after multiple lines of chemotherapy. However, this definition ignores the heterogeneity and complexity of the spectrum of diseases that comprise "platinum resistant ovarian cancer" (PROC) and is innately flawed as it was initially derived using methods of detection of recurrence that would now be regarded as outdated. The outcome of patients with PROC is generally poor, with low response rates to further chemotherapy and a median survival of less than 12 months, but this is unpredictable and can be quite variable from study to study. "

1.2. Elenagen Drug Product

The DNA vaccine, Elenagen, is a double-stranded supercoiled circular plasmid DNA coding for the gene p62 (aka SQSTM1). Elenagen is a solution containing 2.5 mg of the active substance in 1 mL. Ampoules of Elenagen are stored frozen and thawed immediately before use. Via intramuscular injection (deltoid or gluteus as backup), Elenagen is absorbed by cells local to the injection site where it behaves similarly to any other DNA vaccine [1]. Elenagen plasmid DNA enters the nucleus of the patient's cells, where the the gene for p62 is expressed, but not inserted in the chromosome of the cell (**Figure 1**). After entering the cells, the plasmids remain a short time. The plasmids cannot replicate and disappears in less than a month. Plasmids not taken-up by cells are soon degraded by DNases of the body [2].

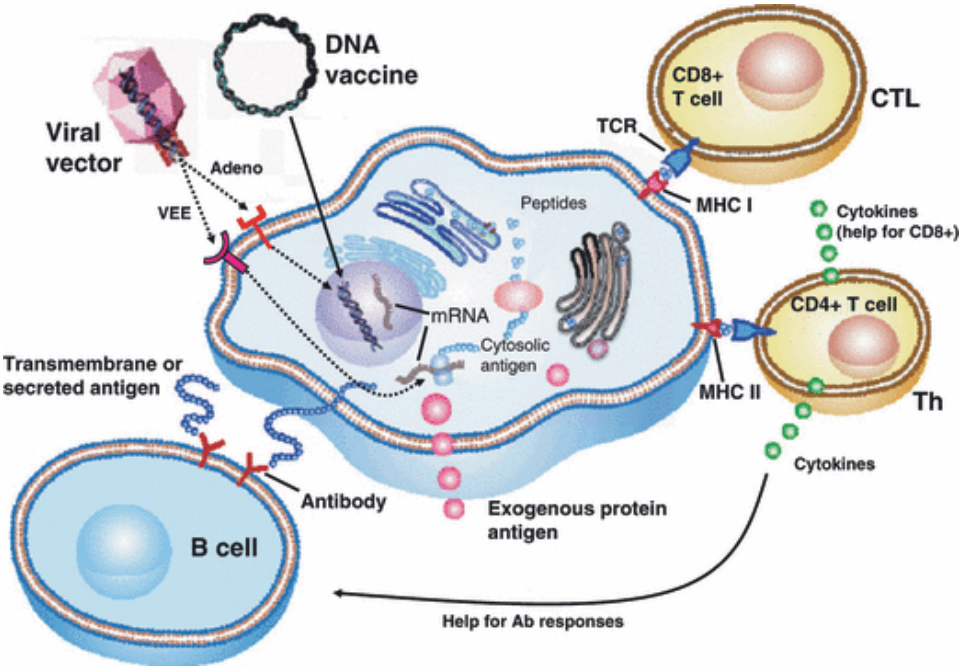


Figure 1. DNA vaccine can generate both T-cell and B-cell immune responses

Elenagen operates through at least two (or more) complementary mechanisms. **First**, Elenagen acts as a classic anti-cancer DNA vaccine. Many types of cancer cells are known to over-express p62 and no other cell types are known to exhibit this behavior making it a unique and attractive target [3]. Moreover, cancer cells do not self regulate or down-regulate expression of p62 because it plays an essential role in both tumor formation and metastasis [4]. Intramuscularly administered Elenagen induces an adaptive immune response to the over-expressed protein p62 thus evoking an immune response against cancer cells (**Figure 1**).

Second, Elenagen exhibits an anti-inflammatory effect [5,6] (**Figure 2**). In contrast to acute inflammation that is beneficial for immune response to microbes and cancer cells, chronic inflammation is detrimental. In particular, intratumoral chronic inflammation disables immune cells and suppresses anti-tumor immunity [7,8]. Given that most chemotherapeutics (at least partially) leverage the immune system as part of their anti-tumoral mechanism of action, chronic inflammation decreases sensitivity to chemotherapy and prevents drugs delivery to tumors [9]. Elenagen lowers chronic inflammation and renders the tumor cells more susceptible to chemotherapy and the immune response by the patient.

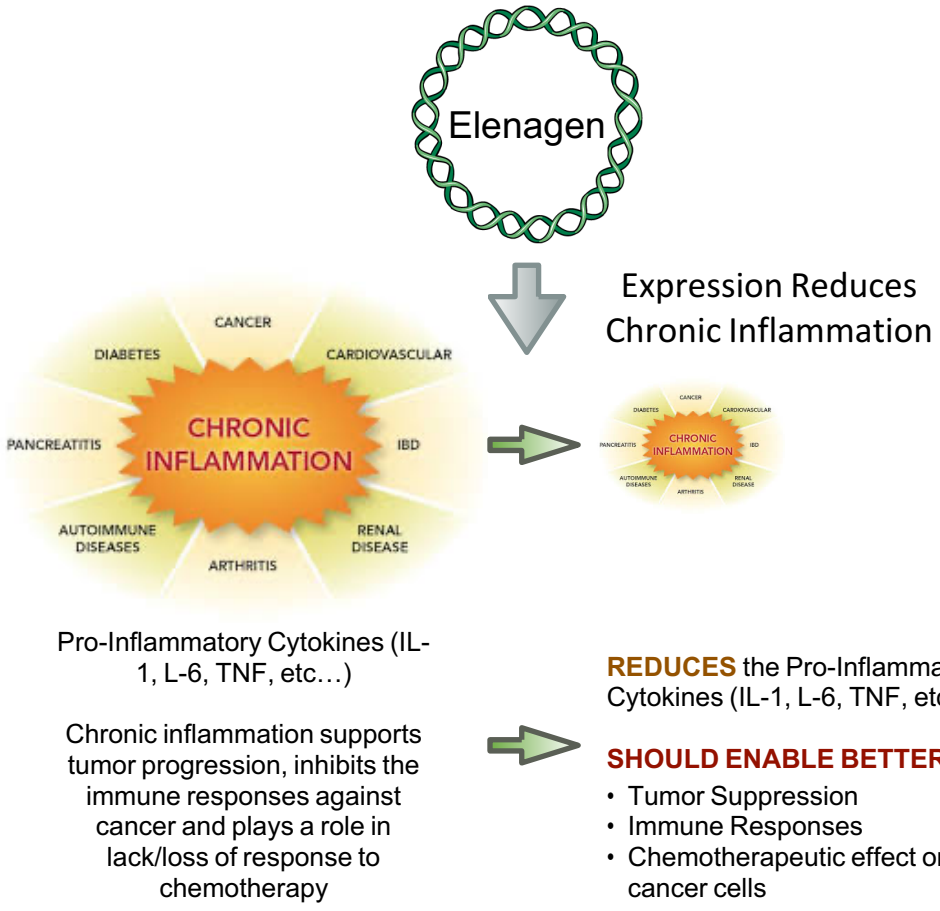


Figure 2. Elenagen blocks chronic inflammation which improves the other mechanisms of action exhibited by Elenagen and chemotherapeutic agents.

Elenagen expression and stimulation of the various feedback loops also results in changes to the internal structure of the tumor and has shown promise in lowering the grade of the tumor [10]. This may contribute to sensitization to chemotherapy that was observed in the first Ph 1/2 trial. Also of particular importance, Elenagen treatment dramatically changes expression of collagen isoforms [10], making it easier for tumor infiltrating lymphocytes (TILs) to enter the tumor, and harder for metastatic cells to exit.

Therefore, these two mechanisms of Elenagen action are complimentary and make it and the combination with chemotherapeutic agents a unique anti-cancer therapeutic.

In the phase I/IIa clinical trial, Elenagen was used as a mono-therapy [11]. In that study, Elenagen showed promise in treating patients with advanced disease, for which all standard methods of treatment were exhausted. For example, progression of ovarian cancer was stopped for periods of time in 4 out of 6 patients. Breast cancer patients responded similarly with 4 of 8 patients experiencing a halt in disease progression for meaningful periods. Moreover, an important observation in regard to chemotherapy was made. Patients that had stopped receiving Elenagen and experienced resumed disease progression were started on chemotherapy again. They were patients who previously failed to respond to 5th to 8th lines of chemotherapy. All of these patients that had received Elenagen, responded to the first and/or second-line chemotherapy [11]. This despite the fact that before obtaining Elenagen they were resistant to the same or similar chemotherapy. Most encouraging is a case study of a woman with triple negative breast cancer that received Elenagen and experienced 19 weeks of progression-free disease and partial tumor reduction [12]. This was a patient that previously failed 21 rounds of chemotherapy and was actively progressing at the time of enrollment.

1.2.1. Rationale for the Study

The initial human trial with Elenagen provided strong evidence that a combined approach using Elenagen and a chemotherapy regimen may provide a significant benefit for patients [11]. There are currently no complications expected for the combined use of Elenagen and a chemotherapy regimen.
We expect the combination will:

1) increase progression-free survival;
2) increase overall life expectancy;
3) a partial decrease in the size of tumors and metastases;
4) a decrease in the number and/or frequency of pain medications needed;
5) a decrease in the severity of concomitant comorbid diseases, especially diseases associated with chronic inflammation.

There are other cancer types that have over-expressed p62 and we hope that success in this trial will lead to the development of additional Elenagen-based therapies.

1.2.2. Rationale for choosing the human p62 gene

p62 is over-expressed in multiple types of cancer including Platinum-Resistant Ovarian Cancer. Using the natural human sequence provides the best opportunity to elicit the desired response using a DNA vaccine. The DNA is not integrated and quickly degraded so there is no need for

special markers or recovery technologies.

1.2.3. Rationale for Dose Selected

DNA vaccines do not follow a linear dosing relationship. Multiple doses were evaluated in our preclinical studies. There were no animal deaths and no abnormal health findings related to study drug. The animal studies did demonstrate signs of efficacy and based on those results three dose levels were selected to evaluate in the first clinical trial conducted in Russia. Five patients were evaluated at each dose level including 1 mg, 2.5 mg, and 5 mg injected intramuscularly weekly for 5 weeks. All doses were well tolerated with only Grade 1 AEs observed. There were no observable differences between the doses and the study was not powered sufficiently to assess statistical differences [11]. CureLab has selected the lowest dose, 1 mg weekly, to begin the next phase of assessment as it should be the safest, most efficient dose and resulted in some strong efficacy signals in the previous trial.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

To Assess Efficacy and Safety of Plasmid Elenagen in Combination With Gemcitabine in Patients With Platinum-resistant Ovarian Cancer

2.2. Study Endpoints

2.2.1. Primary Endpoint: PFS

Progression-Free Survival (PFS):

Time to progression of the tumor and/or the transition of the tumor process from the non-resectable to the resectable state.
The criterion for evaluating the effectiveness of progression-free survival (PFS):
The assessment of PFS will be performed from the date of treatment to the first registration of disease progression based on the results of CT examination or death. For the comparison of treatment groups in relation to the PFS the same analytical methods will be applied as in the valuation according to the final criterion of OS.

2.2.2. Safety and Efficacy Endpoints

SAFETY

- Incidence of treatment related mortality

- Monitoring of laboratory parameters and frequency and severity of clinical AEs and SAEs, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

RECIST

Immediate effectiveness of treatment in accordance with the criteria of response evaluation criteria in solid tumors (RECIST) 1.1

Overall survival (OS)

Criterion for evaluating the effectiveness of overall survival (OS)

OS is defined as the length of time from the date of treatment to the date of death. If no fatal outcome is recorded during the study, the time period will be limited to the last day on which the patient was known to be alive, or the date on which clinical data collection is completed, whichever comes first. As part of the analysis of the final evaluation OS criterion, the comparison of the 3 treatment groups will be carried out using a stratified logarithmic rank criterion using 3 stratification factors. The hazard ratio (HR) with the corresponding 2-sided 95% confidence intervals (CI) will be assessed using the stratified Cox proportional hazards model (CPH). Survival for each group will be presented using Kaplan-Meier curves, followed by a description in terms of median and probability of survival in 3, 6, 9 and 12 months, with corresponding 2-sided 95% CI for these estimates.

2.3. Overall Plan and Design of Study

This is a randomized, open label, multi-site, weekly dose Phase II study in up to 40 adults with Platinum-Resistant Ovarian Cancer. The purpose is to evaluate weekly intramuscular injections of Elenagen (plasmid encoding the gene for human protein p62) in conjunction with 1 of 2 possible chemotherapeutic regimens administered per product insert and physicians' best judgement. Total duration is 52 weeks. Eligible patients may have the option to continue on a separate extension study to continue to receive chemotherapy and Elenagen for one additional year.

All patients will receive chemotherapy:

Cohort 1 – Gemcitabine + Placebo

40 Subjects Total:

20 Subjects Gemcitabine + Placebo

Gemcitabine 800 mg/m^2 administered on day 1 and day 8 of a 21 day cycle, IV

Placebo – administered weekly via 1.1 mL intramuscular injection (deltoid or gluteus as backup)

Cohort 2 – Gemcitabine + Elenagen

20 Subjects Gemcitabine + Elenagen

Gemcitabine 800 mg/m^2 administered on day 1 and day 8 of a 21 day cycle, IV

Elenagen, 2.5 mg/mL - administered weekly via 1.1 mL intramuscular injection (deltoid or gluteus as backup)

Each course of therapy runs every 21d (gemcitabine) from the start of the previous. Evaluation of the therapeutic effect (computer tomography) is carried out 12-14 days after completion of each 3rd cycle of chemotherapy (before the 4-, 7-, 10-th courses and on final visit for completion of

treatment, and, if required, on the follow-up visits). In the absence of tumor progression, the effectiveness of treatment (computer tomography) is evaluated every 6 weeks (follow-up visits). If CT data at any of these stages marked tumor regression with the transition of the tumor process in a resectable state, it will be possible to perform surgery at any time of treatment. Patients after surgery are evaluated separately. Duration of chemotherapy treatment is at least 6 cycles and then at physicians' discretion.

Study procedures will include efficacy and safety assessments.

2.4. Data Monitoring Committee

A Data Monitoring Committee (DMC) comprised of members with appropriate scientific and medical expertise to monitor the study will be convened before the study is opened. A charter describing the composition and conduct of the DMC will be issued by the Sponsor and agreed to by all DMC members prior to the DMC's initial meeting.

A DMC chairperson will be appointed who will be responsible for the overall operation of the DMC. Minutes from each meeting will be recorded and archived.

The DMC will meet by teleconference at regular intervals, approximately once every 3 months, or more frequently if needed, and depending on speed of subject enrollment and amount of new data generated.

It will be the responsibility of the Sponsor or Sponsor's designee to promptly contact the chairperson of the DMC about any clinically meaningful AE (i.e., unexpected in nature and / or in severity).

The DMC will have the right to halt the study at any time due to concerns for the safety of the subjects.

2.5. Treatment Discontinuation and Enrollment Suspension Criteria

2.5.1. Enrollment Suspension Criteria

Enrollment in this study may be stopped at any time for safety reasons. The Sponsor will inform the regulatory authorities and the Investigators, and each site's Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and other appropriate institutional regulatory bodies will be promptly notified if a decision to suspend enrollment is made. In the event enrollment is suspended, subjects who have already been treated with Elenagen- Drug Product will continue in the study unless a specific decision is made otherwise.

The following are examples of events that may result in enrollment suspension. In each case, the event will trigger an assessment by the DMC, followed by a recommendation as to whether the study should continue without change, continue with specific changes, or terminate:

- Death related to Elenagen Drug Product
- Determination of unexpected, clinically significant, or unacceptable risk to subjects (e.g., development of study treatment-related Grade 3 or 4 toxicities in at least 3 subjects)

3. STUDY POPULATION

3.1. Number of Subjects

Up to 40 subjects with platinum-resistant ovarian cancer are to be enrolled. Subjects who withdraw prior to treatment with Elenagen may be replaced.

3.2. Inclusion Criteria

1. The patient, female, is 18-70 years old at the time of consent
2. Written informed consent of the patient to participate in clinical trials
3. Presence of confirmed ovarian cancer
4. Presence of measurable tumor lesions according to RECIST 1.1 criteria
5. Functional status on Eastern Cooperative Oncology Group (ECOG) scale 0 - 2
6. Life expectancy of at least 6 months
7. Adequate function of the organs as determined by the following criteria:
   - Absolute number of neutrophils (ACHN) ≥1500/mm3 (≥1.5 × 109/l)
   - Platelet count ≥100,000/mm3 (IU: ≥100 × 109/l)
   - Hemoglobin level ≥ 9.0 g/DL; analysis performed ≥ 2 weeks after the last hemotransfusion
   - Level of AST and ALT blood serum, not exceeding 3x the upper limit of the norm
   - Level of serum bilirubin, not exceeding 1.5x the upper limit of normal
8. Subject is able to follow directions of the research physician and follow the study regimen
9. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

3.3. Exclusion Criteria

1. Platinum-sensitive relapse of ovarian cancer (disease recurrence occurred more than 6 months after the last administration of platinum drug(s)
2. Presence of serious diseases or health conditions:
   - Other malignancies, with the exception of malignancies, treated more than 3 years ago without signs of return of the disease

- Brain metastases or leptomeningeal metastases if disease is not stable after treatment and patient is still on corticosteroids to control symptoms from brain metastases
- Active infection (e.g. fever ≥ 38°C), including active or unresolved pneumonia/pneumonitis
- Uncontrolled diabetes mellitus
- Myocardial infarction in the last 3 months, severe/unstable angina, clinically manifested heart failure class III-IV according to the classification of the New York Cardiology Association (NYCA)
- Gastrointestinal bleeding within the last 2 weeks
- Human immunodeficiency virus (HIV), chronic or acute hepatitis B or hepatitis C (Note: if hepatitis is chronic, but there is no active HBsAg and no positive Hepatitis C RNA, then the subject may be enrolled)
- Patients with autoimmune disorders or organ transplantation who require immunosuppressive therapy
- Mental illness that may increase the risk associated with participation in the study or taking the study drug or that may affect the interpretation of the results of the study
- Polyallergy, bronchial asthma in history

3. Pregnancy and lactation
    - Patients of childbearing age included in the study should be informed about the need to comply with adequate contraception throughout the study
4. Major surgery during the previous 4 weeks
5. Previous chemotherapeutic treatment of the patient with Gemcitabine
6. Radiotherapy with extended field radiation within the previous 4 weeks or radiotherapy with a limited field radiation within the previous 2 weeks
7. Use of an investigatory drug within 14 days or 5-half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 day of receiving the first dose of study drug
8. Individual intolerance to the drug
9. Patients cannot be enrolled in a chemotherapy cohort where they have previously received that chemotherapy. They may participate if they are enrolled in a cohort with a different chemotherapy than previously treated with

3.4. Subject Screening and Registration

Subjects willing to participate in the study will provide written informed consent according to Good Clinical Practice (GCP). Written informed consent must be obtained before the conduct of any Screening tests.

Upon signing the informed consent, the subject will be registered and assigned a unique subject number. Once a subject number has been assigned, it cannot be reused, and the number stays with the subject even if the subject is subsequently determined to be ineligible for the study.

3.5. Subject Withdrawal from the Study

Subjects have the right to withdraw from the study at any time for any reason.

After giving informed consent, subjects may withdraw or be withdrawn from study-related procedures and treatments at any time under the following conditions:

- Withdrawal of consent
- The subject is unable to comply with protocol-defined visits
- Any medical condition which, in the opinion of the investigators, would put the subject at risk for continuing treatment or follow-up studies

Subjects withdrawn from the study prior to treatment with Elenagen Drug Product may be replaced. Subjects who receive Elenagen Drug Product but are subsequently withdrawn will not be replaced.

4. STUDY TREATMENTS

4.1. Description of Elenagen Drug Product

Elenagen is the preparation of plasmid encoding the gene for human p62 protein. It is manufactured and released as ampoules containing 1.1 mL of 2.5 mg/mL plasmid in PBS and kept frozen at -20C until it is thawed just prior to injection. One ampoule is used per subject dose (2.5 mg Elenagen dosed via 1.0 mL intramuscular injection).

4.2. Summary of Treatments to be Performed or Administered

4.2.1. Dose and Administration

Prior to administration, one ampoule of Elenagen Drug Product is thawed and immediately injected intramuscularly (deltoid or gluteus as backup) using aseptic techniques by trained personnel.

4.3. Method of Assigning Subjects

Subjects entered into the study will be randomized to 1 of 2 chemotherapy cohorts and with or without Elenagen in this open-label study.

4.4. Binding, Packaging and Labeling

4.4.1. Blinding and Breaking the Blind

This is an unblinded, open-label study.

4.4.2. Packaging and Labeling

Elenagen is manufactured ready to use in glass ampoules and labeled appropriately for the study.

4.5. Duration of Subject Participation

Each subject is planned to remain on study for 52 weeks from time of consent and then, if eligible, will be asked to participate in an extension study for one additional year.

4.6. Assessment of Treatment Compliance

Eligible subjects will receive Elenagen Drug Product as in-patients and thus will be monitored by hospital personnel.

4.7. Product Accountability

Elenagen Drug Product accountability and traceability is ultimately the responsibility of the Investigator and Sponsor. However, this responsibility may be delegated to suitably qualified personnel listed on Food and Drug Administration (FDA) Form 1572 who has had appropriate study-specific training and whose name has been appropriately listed on the Delegation of Responsibility Log for this task.

Detailed records will be maintained to allow for accurate accountability of the Elenagen Drug Product as per applicable sponsor and clinical site procedures. These records will include details of storage of the Elenagen Drug Product, administration to subjects, and disposal of remaining materials.

All material containing Elenagen Drug Product will be treated and disposed of as hazardous waste in accordance with governing regulations and clinical site procedures.

4.8. Prior and Concomitant Medication

4.8.1. Prior Medication

All medications taken within 30 days prior to the Screening Visit are to be recorded in the Prior and Concomitant Medication CRF.

4.8.2. Concomitant Medications and Therapies

All concomitant medications and therapies (ie, those that are taken by the subject after signing the informed consent form) will be recorded in the Concomitant Medication CRF.

Instructions and/or restrictions regarding specific concomitant medications and therapies are listed below. Concomitant medications and therapies not explicitly listed below may be used at the discretion of the treating physician and as per local standard of care.

- Investigational agents are excluded and must be discontinued 30 days before Screening.

4.8.3. Infection Surveillance and Prophylaxis

Institutional practices and investigators best judgment should be used recognizing the potential immune-complications with chemotherapy and potential unknown effects of Elenagen in combination with the three chemotherapeutic agents being evaluated in this study.

5. STUDY ASSESSMENTS

5.1. Schedule of Events

Detailed descriptions of the efficacy, pharmacodynamics, and safety procedures to be conducted during this study are provided in the following subsections. Additional details, including administrative information, will be provided in the Study Operations Manual. Evaluations and procedures identified in the Schedule of Events may be performed at unscheduled visits, as clinically indicated, at the Investigator's discretion in consultation with the Sponsor.

5.1.1. Screening and Baseline

Assess subject suitability for the study including assessment of inclusion/exclusion criteria. Prior to all clinical trial procedures, a signed informed consent (IC) is required. The duration of screening should not exceed 10 days. Blood samples for clinical laboratory tests, including hematology, serum chemistry, liver function tests, coagulation studies, and iron studies, are to be

collected per the Schedule of Events. These tests are to be performed by the local laboratory, and reviewed by the Investigator or qualified designee (e.g., physician’s assistant, nurse practitioner).

Table 1. Screening + Baseline

Procedure	Screening (10d max)
Signing of informed consent form (ICF)	X
Demographics	X
Medical History	X
Physical Examination	X[1]
Vital Signs	X
Local lab: Blood for clinical laboratory tests	X[2]
Local lab: Urinalysis	X
Local lab: Blood for serology	X
Local lab: Blood for immunological studies	X[3]
Local lab: Blood for serum β-human chorionic gonadotropin for women of child-bearing potential (WOCBP; serum pregnancy test)	X
Computed tomography with contrast of the brain, chest, abdomen, pelvis, osteoscintigraphy or positron emission tomography of the whole body (PET-CT)	X

[1] At Screening, physical examination includes height, weight, analysis of the general condition of the patient on the ECOG scale, determination of body temperature and heart rate, blood pressure, respiratory rate, ECG

[2] Including HIV-1, HIV-2, HBcAb, HBsAb, HBsAg, HCV antibody, HTLV-1, HTLV-2, syphilis (RPR), toxoplasmosis, Trypanosoma cruzi, and West Nile Virus

[3] T cell subsets [CD4, CD8], B cells, natural killer cells, and antibody titers against tetanus, pneumococcus, and measles/mumps/rubella

After the screening stage is completed, patients are assigned to a cohort based on institutional standards and treating physicians best judgment. Patients will be randomized using a centralized system for plus/minus Elenagen. The maximum allowable period between screening and the first course of treatment is 28 days, otherwise the screening assessments must be completed again.

5.1.2. Day 1 (Dosing)

Clinical examination of the patient (analysis of the general condition of the patient on the ECOG scale, determination of body temperature and heart rate, blood pressure, respiratory rate).

A course of chemotherapy according to the scheme of randomization

Monitoring of body functions:

- Evaluation of vital signs (before administration of drugs)
- Determination of body temperature and blood pressure before administration of drugs, as well as 30 minutes after administration of drugs
- Ensure an appropriate record of related procedures is kept
- Record and notify appropriate individuals of any adverse events during and after administration of the drug

5.1.3. Schedule of Assessments

Table 3. Schedule of Assessments

Procedure:	Screen (Baseline)	Visits (to be based on Standard of Care Course Frequency over 26 weeks)						Final (3wks post last course)
		1	2	3	4	5	6	
Written informed consent[1]	+							
Histological confirmation of diagnosis	+							
Medical anamnesis (history)	+							
Assessment of BRCA mutation status	+							
Height	+							
Functional status: ECOG[2]	+	+	+	+	+	+	+	+
Medical examination[3]	+	+	+	+	+	+	+	+
Urine analysis[4]	+	+	+	+	+	+	+	+
General blood test[5]	+	+	+	+	+	+	+	+

Biochemical analysis of blood[7]	+	+	+	+	+	+	+	+
A pregnancy test[8]	+	+	+	+	+	+	+	+
Indicators of basic vital functions[9]	+	+	+	+	+	+	+	+
Body weight[10]	+	+	+	+	+	+	+	+
EKG[11]	+	+	+	+	+	+	+	+
Concomitant therapy[12]	+	+	+	+	+	+	+	+
CT[13] *	+	-	-	-	+	-	-	+
Assessement of AE/SAE	+	+	+	+	+	+	+	+
Chemotherapy	-	+	+	+	+	+	+	-

*On visits of screening and completion of treatment CT of chest, abdomen, pelvis, and brain is performed. On other visits – CT of affected areas.

1. Written informed consent must be obtained prior to any research procedures.

2. Functional status according to the criteria of the Eastern United group of oncologists (Eastern Cooperative Oncology Group, ECOG): to determine at the time of randomization (within 3 calendar days before treatment with the study drug, on the 1st day of the 1st course of treatment and on the 1st day for all subsequent cycles).

3. Medical examination: general condition, general examination, evaluation of skin, eyes, ears/throat/nose, head and neck, heart, chest and lungs, abdomen, limbs, lymph nodes, musculoskeletal system, respiratory nervous system, cardiovascular system, genitourinary system.

4. Urine analysis: bilirubin, erythrocytes, glucose, ketone bodies, leukocytes, pH, protein, specific gravity.

5. General blood test: erythrocytes, hemoglobin, platelets, hematocrit, leukocytes with the formula.

6. Biochemical analysis of blood serum: Na, K, Cl, urea, total protein, alkaline phosphatase, AST, ALT, glucose, total bilirubin, direct bilirubin, creatinine.

7. A pregnancy test: during screening – blood serum, on other visits – urine.

9. Indicators of basic vital functions: blood pressure, respiratory rate, pulse and body temperature are determined in patients in a sitting position, after they stay at rest for 10 minutes. The date and time of the examination should be indicated in the medical history.

10. Body weight is determined before each course of chemotherapy.

11. EKG in 12 leads.

12. Registration of all data on previous and concomitant therapy and use of medicines.

13. CT of chest, abdomen, pelvis, and brain – slice of ≤ 5 mm with i.v. enhancement. On the 1-,2-,3-,5-,6-visits, patients will not have CTs, on the 4-,7- visits, patients will have CTs.

5.2. Dosing Procedures

Table 4. Study Drug Dosing Procedures

Drug	Day	Dose	Dilution	Administration
Gemcitabine 21 day cycle	**d1**	800 mg/m^2 (±10 mg)	Diluted in 100 - 500 mL of 0.9% NaCl (prepared solution of 0.1 mg/mL can be stored at room temperature up to 24 hours)	The drug is administered iv within 30 minutes
	d8	800 mg/m^2 (±10 mg)	Diluted in 100 - 500 mL of 0.9% NaCl (prepared solution of 0.1 mg/mL can be stored at room temperature up to 24 hours)	The drug is administered iv within 30 minutes
Elenagen	**24-48 h before chemotherapy, then once a week w/o stopping**	1.0 mL		Before use, thaw one ampoule. Inject 1.0 mL intramuscularly (deltoid or gluteus as backup)
The interval between courses is 2 weeks, i.e. the next course starts on the 28th day from the beginning of the previous course.				

5.2.1. Gemcitabine Dosing

The recommended dosage of GEMZAR is 1000 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle however it may be prudent to start with 800 mg/m^2 in this patient population.

Emetogenicity of Gemcitabine is low. Some patients experience nausea and vomiting. In such cases administration of metoclopramide 1 to 2 mg/kg/dose (depending on the emetogenic potential of the agent) IV infused over a period of not less than 15 minutes, 30 minutes before administration of chemotherapy.

Subsequent doses: The dose should be repeated every 2 hours for 2 doses following the initial dose, then every 3 hours for 3 additional doses.

Nonhematologic toxicity (all indications):
Hold or decrease gemcitabine dose by 50% for the following: Severe (grade 3 or 4) nonhematologic toxicity until resolved (excludes nausea, vomiting, or alopecia [no dose modifications recommended])
Permanently discontinue gemcitabine for any of the following: Unexplained dyspnea (or other evidence of severe pulmonary toxicity), severe hepatotoxicity, hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), posterior reversible encephalopathy syndrome (PRES).

Table 5. Gemcitabine dose modification for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	**Absolute NeutrophilCount ($x10^6$/L)**		**Platelet Count ($x10^6$/L)**	**Dose Modification**
Day 1	≥ 1500	and	≥ 100,000	None
	< 1500	or	< 100,000	Delay Treatment Cycle
Day 8	≥ 1500	and	≥ 100,000	None
	1000 to 1499	or	75,000 to 99,999	50% of full dose
	< 1000	or	< 75,000	Hold

Table 6. Recommended Dosage Modifications for GEMZAR for Myelosuppression in Previous Cycle in Ovarian Cancer

Occurrence	Myelosuppression During Treatment Cycle	**Dose Modification**
Initial Occurrence	• Absolute neutrophil count less than 500 x 10^6/L for more than 5 days or • Absolute neutrophil count less than 100 x 10^6/L for more than 3 days or • Febrile neutropenia or • Platelets less than 25,000x10^6/L or • Cycle delay for more than one week due to toxicity	Permanently reduce GEMZAR to 800 mg/m^2 on Days 1 and 8

Subsequent Occurrence	If any of the above toxicities occur after the initial dose reduction:	Permanently reduce GEMZAR to 800 mg/m^2 on Day 1 only

Table 7. Gemcitabine dose modification due to hepatotoxicity

Bilirubin		**AST/ALT**	Gemcitabine
		2 - 3 ULN*	75%
20 - 50	and/or	> 3	50%
51 - 85	and/or	any	25%
> 85	and/or	any	Cancel

***-** the upper limit of normal

Table 8. Gemcitabine dose modification in connection with nephrotoxicity

Creatine Clearance (mL/min)	**Gemcitabine Dose**
> 50	100%
30 - 49	75%
< 30	50%

Table 9. Gemcitabine dose modification in connection with stomatitis

Degree of manifestation	**Actions**
2 Painful hyperemia, ulceration of the mucous membrane, the patient can take food	Delay treatment until the toxicity is resolved. With subsequent administration, use a 100% Gemcitabine dose
3 Painful hyperemia, ulceration of the mucous membrane, the patient can NOT take food	Delay treatment until the toxicity is resolved. With subsequent administration, use a 75% Gemcitabine dose

4 Necrosis of the mucous membrane, requires parenteral nutrition	Delay treatment until the toxicity is resolved. With subsequent administration, use a 75% Gemcitabine dose

Table 10. Gemcitabine dose modification due to diarrhea

Degree of manifestation	Actions
2 Stool 4-6 times a day	Postpone treatment until toxicity is resolved. With subsequent administration use 100% Gemcitabine dose.
3 + 4 Stool more than 7 times a day, life-threatening condition	Postpone treatment until toxicity is resolved. With subsequent administration use 75% (3) or 50% (4) Gemcitabine dose.

Extravasion - Gemcitabine - Neutral Action

5.2.2. Elenagen-Dosing

Elenagen will be administered 24-48 hours before receiving their scheduled chemotherapy (Gemcitabine), then once a week every week for the duration of the trial.

Before use, thaw one ampoule of Elenagen that contains plasmid at 2.5 mg/mL in PBS. Inject 1.1 mL intramuscularly (deltoid or gluteus as backup) to deliver 2.5 mg.

Table 15. Elenagen dose modification in connection with site-injection irritation

Toxicity	Dose Adjustment
Mild Irritation	Monitor
Medium Irritation	Change injection site to opposite side and monitor for to evaluate cause
Severe irritation	Change injection site to opposite side and carefully monitor both original injection site and new site to evaluate cause

Table 16. Elenagen dose modification in connection with AEs or SAEs

Toxicity	Dose Adjustment
AE	Treat and Monitor; report AE immediately
SAE	Report immediately; skip dosing until course of action is resolved

Study Measures

Treatment of subjects in this clinical trial will have a verified diagnosis of platinum-resistant ovarian cancer and will be carried out in accordance with the requirements, regulations, guidelines and other documents that determine the type of treatment, volume of therapeutic measures and their sequence of administration. This study will include a prescreening period, a screening period, a randomization period, a treatment period, and a follow-up period (i.e. study regimen).

5.2.3. Demographics and Medical History

Subject demographic data such as gender, age, race, and ethnicity, will be obtained at Screening, as per the Schedule of Events.

A complete medical history, including history of cancer diagnosis and treatment will be obtained at screening, as per the Schedule of Events. The medical history is to include all prior and current medical history.

5.2.4. Physical Examination and Performance Status

A physical examination (general appearance; head eyes, ears, nose, and throat; cardiovascular; dermatologic, abdominal; genitourinary; lymph nodes; hepatic; musculoskeletal; respiratory; and neurological) is to be performed, assessed per the Schedule of Events.

Weight and height are also to be measured at Screening, as per the Schedule of Events.

5.2.5. Vital Signs

Vital signs, including systolic/diastolic blood pressure, pulse, respiration rate, temperature, and oxygen saturation are to be measured per the Schedule of Events.

5.2.6. Clinical Laboratory Tests

Blood samples for clinical laboratory tests, including hematology, serum chemistry, and other , tests included in the protocol (see **Table 2**) are to be collected per the Schedule of Events. These tests are to be performed by the local laboratory, and reviewed by the Investigator or qualified designee (e.g., physician's assistant, nurse practitioner).

Vital signs, including systolic/diastolic blood pressure, pulse, respiration rate, temperature, and oxygen saturation are to be measured per the Schedule of Events.

5.2.7. Clinical Laboratory Tests

Blood samples for clinical laboratory tests, including hematology, serum chemistry, and other , tests included in the protocol (see **Table 2**) are to be collected per the Schedule of Events. These tests are to be performed by the local laboratory, and reviewed by the Investigator or qualified designee (e.g., physician's assistant, nurse practitioner).

5.2.8. Adverse Event Assessments

Monitoring of AEs will be conducted throughout the study. AEs, as defined in Section 7, will be monitored and recorded in the CRFs from the time informed consent is signed through the following timepoints:

- ≥Grade 1 AEs: through 30 days after Elenagen Drug Product infusion
- ≥Grade 2 AEs: through 12 months after Elenagen Drug Product infusion
- Serious adverse events (SAEs) and Elenagen Drug Product-related AEs: through 12 months after Elenagen Drug Product first dose.

For subjects who discontinue from the study for reasons other than withdrawal of consent before infusion of drug product, follow-up for AEs is required for 30 days post-discontinuation.

All AEs should be monitored until they are resolved or are clearly determined by the Investigator to be due to a subject's stable or chronic condition or inter-current illness(es).

6. ADVERSE EVENTS

6.1. Definitions, Documentation, and Reporting

6.1.1. Adverse Events

An AE is any change in physical signs, symptoms, and/or clinically significant laboratory change occurring in any phase of a clinical study regardless of its relationship to study drug. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions. A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the informed consent form and is documented as part of the subject's medical history.

6.1.2. Unexpected Adverse Events

An AE is considered unexpected with Elenagen Drug Product if it is not consistent in nature or severity with information contained in the written information or current Investigator's Brochure provided to the Investigator by the Sponsor.

6.1.3. Serious Adverse Events (SAEs)

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form
- Requires in subject hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned)
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a subject's ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event
    - An important medical event is an event that may not result in death, be life- threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs.

6.2. Adverse Event Assessment

For both serious and non-serious AEs, the Investigator must determine both the intensity of the event and the relationship of the event to Elenagen Drug Product administration.

Intensity will be assessed by the Investigator using the NCI CTCAE, version 5.0. If the AE is not included in the CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

Grade	Definition
Mild (Grade 1)	The AE is noticeable to the subject, but does not interfere with routine activity.
Moderate (Grade 2)	The AE interferes with routine activity, but responds to symptomatic therapy or rest.
Severe (Grade 3)	The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy
Life-Threatening (Grade 4)	The subject is at immediate risk of death.
Death (Grade 5)	Death

If the intensity (grade) changes within a day, the maximum intensity (grade) should be recorded. Relationship will be determined by the Investigator according to the criteria that follow. Relationship of AEs to Elenagen Drug Product will be determined after the start of Elenagen Drug Product infusion on Day 0; prior to that time, relationship to study treatment other than Elenagen Drug Product will be assessed:

Investigator Assessment	Definition	Classification for Reporting Purposes
Not Related	Exposure to the drug product did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the drug product.	Not Related
Unlikely Related	The study treatment and the AE were not closely related in time, and/or the AE could be explained more consistently by causes other than exposure to the drug product.	
Possibly Related	The study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the drug product.	Related
Related	The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the drug product than by other causes, or the drug product was the most likely cause of the AE.	

6.3. Procedures for AE and SAE Collection and Reporting to Sponsor

Each subject must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, laboratory assessments, observations of

study personnel, and spontaneous reports from subjects.

All AEs (serious and non-serious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the course of the study must be promptly reported, with completed SAE forms submitted, by the Investigator to the Medical Monitor within 1 working day from the point in time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not they are considered causally related to Elenagen Drug Product. SAE forms, created specifically by the Sponsor, will be provided to each clinical site however SAEs should preferentially be entered into the SAE eCRF. The information collected will include subject number, a narrative description of the event and an assessment by the Investigator as to the severity of the event and relatedness to Elenagen Drug Product. A sample of the SAE form can be found in the SOM. Follow-up information on the SAE may be requested by the Sponsor.

If there are serious, unexpected adverse drug reactions associated with the use of Elenagen Drug Product, the Sponsor will notify the appropriate regulatory agency(ies) and all participating investigators on an expedited basis and in accordance with applicable regulations. It is the responsibility of the Investigator to promptly notify the IRB/IEC and other appropriate institutional regulatory bodies of all unexpected serious adverse drug reactions involving risk to human subjects

6.4. Pregnancy and Contraception

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., spontaneous abortion, which may qualify as an SAE). However, all pregnancies occurring during this study (in subjects or female partners of subjects) are to be reported in the same time frame as SAEs using the Pregnancy Form. The course of all pregnancies, including perinatal and neonatal outcome, regardless of whether the subject has discontinued participation in the study, will be followed until resolution, including follow-up of the health status of the newborn to 6 weeks of age.

The effects of administration of Elenagen Drug Product on the pregnant female or the developing fetus are unknown. Female subjects of child-bearing potential are required to use effective contraception during the entirety of the study (1 year).

6.5. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or to follow-up on AEs or as deemed necessary by the Investigator. Evaluations and procedures to be performed at unscheduled visits, as clinically indicated at the Investigator's discretion in consultation with the Sponsor, and may be based on those listed in the Schedule of

Events.

6.6. Extension Protocol

All subjects will be followed for 52 weeks of weekly dosing under this protocol. Thereafter, eligible subjects will be asked to enroll in a distinct extension protocol to continue receiving Elenagen and chemotherapy for an additional 1 year, with a focus on long-term safety and overall survival outcomes.

7. STATISTICAL PROCEDURES

7.1. Sample Size Estimation

Group 1 – chemotherapy only

Group 2 – chemotherapy + Elenagen

Expected PFS in group 1, according to literature and clinical practice, is 3 mo

Expected PFS with chemotherapy + Elenagen = 8 mo

Therefore, expected Hazard Ratio= 0.38

Given:

- 1:1 randomization,
- Follow-up long enough that nearly all patients progress (i.e., event rate ≈ 100%)
- Power = 0.8; p = 0.05

Sample per group should be 17.

Given that some patients may be unavailable for final analysis, initial inclusion of some extra patients looks appropriate; thus each of our groups consists of 20 patients.

7.2. Populations for Analysis

2 Cohorts of different chemotherapies with and without Elenagen; 20 subjects per group, 40 patients total.

7.3. Procedures for Handling Missing, Unused, and Spurious Data

No imputation will be performed for missing data elements. Every effort will be made to obtain appropriate safety data related to dosing, as well as efficacy data for the 52 week study period.

Sensitivity analyses will be performed to determine the impact of missing efficacy data, such analyses to be outlined in the formal statistical analysis plan.

When tabulating AE data, partial dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment.

7.4. Statistical Methods

7.4.1. General Methods

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of observations, mean, median, standard deviation, minimum and maximum values will be presented.

Descriptive summary statistics as well as 2-sided, 95% confidence intervals will be presented on selected parameters. By-subject listings of data for all completed and discontinued subjects will be provided.

For disease-specific biological parameters and clinical events, baseline will be defined as the average of these parameters over the 2 years before the trial. For other change from baseline analyses, baseline will be defined as the value closest to, but prior to the trial. Longitudinal data (collected serially over time on study and follow-up) will be presented by appropriate time intervals, such as monthly, quarterly and so forth, depending on the nature of the data.

7.4.2. Disposition of Subjects

A tabulation of the disposition of subjects will be presented, including the number enrolled, the number with any after drug product dosing data available for analysis, and the extent of data available. Tables and listings will be provided for subjects in each analysis data set. Subject data will also be displayed by site. The number of subjects completing the study through 52 weeks and reasons for study discontinuation will be reported. Deviations from protocol treatment and assessment specifications will be tabulated and listed.

7.4.3. Demographic and Baseline Characteristics

The following demographic and baseline characteristic factors will be summarized: age (current and age at diagnosis), country of origin, race and ethnicity, time from diagnosis to confirmation for inclusion in the study, method of diagnosis of disease, and the presence of any significant co-morbid conditions. Baseline values of all clinical efficacy parameters will be included in tables of

baseline, post-baseline and change from baseline, with all individual data included in the summary statistics included in by-patient, by-time data listings.

7.4.4. Efficacy Analysis

Criterion for evaluating the effectiveness of overall survival (OS) OS is defined as the length of time from the date of randomization to the date of death. If no fatal outcome is recorded during the study, the time period will be limited to the last day on which the patient was known to be alive, or the date on which clinical data collection is completed, whichever comes first. As part of the analysis of the primary final evaluation OS criterion, the comparison of the two treatment groups will be carried out using a stratified logarithmic rank criterion using 3 stratification factors in randomization according to the treatment prescribed by the randomization system. The risk ratio (RR) with the corresponding 2-sided 95% confidence intervals (CI) will be assessed using the stratified Cox proportional hazards model (CPH). Survival for each group will be presented using Kaplan-Meier curves, followed by a description in terms of median and probability of survival in 3, 6, 9 and 12 months, with corresponding 2-sided 95% CI for these estimates.

The criterion for evaluating the effectiveness of progression-free survival (PFS).

The assessment of PFS will be performed from the date of randomization to the first registration of disease progression based on the results of CT examination or death. For the comparison of treatment groups in relation to the PFS the same analytical methods will be applied as in the valuation according to the final criterion of OS.

7.4.5. Safety Analysis

The safety analyses will include evaluation of the incidence of treatment emergent AEs by preferred term and body system coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized for those events that occur from the 1st day of Elenagen Drug Product dosing (Day 0) through 52 weeks after drug product dosing began (all AEs); All AEs will be listed in by-patients and by-time data listings.

7.5. Procedures for Reporting Deviations to the Statistical Analysis Plan

All deviations from the final statistical analysis plan will be provided in the final clinical study report.

8. ADMINISTRATIVE REQUIREMENTS

8.1. Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of Elenagen Drug Product as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

8.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC and other appropriate institutional regulatory bodies will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC and other appropriate institutional regulatory body approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC and other appropriate institutional regulatory bodies by the Investigator.

8.3. Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or his/her legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

8.4. Subject Confidentiality

In order to maintain subject privacy, all CRFs, accountability records, study reports, and communications will identify the subject by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Laboratory measures will be compared with their corresponding normal ranges and the incidence of abnormally high and abnormally low laboratory values will be calculated for each relevant protocol-specified laboratory test; changes in laboratory parameters over time will be summarized with descriptive statistics, including shifts relative to CTCAE criteria for laboratory abnormalities.

Additional tabulations of safety data may be produced, as warranted by the data. All safety data will be listed.

8.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor, and given approval/favorable opinion by the IRB/IEC and other appropriate institutional regulatory bodies. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC and other appropriate institutional regulatory body approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and

approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC and other appropriate institutional regulatory bodies. The Sponsor will submit all protocol modifications to the regulatory authority in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the CRF and source documentation.

8.6. Direct Access to Source Data

Monitoring and auditing procedures developed by the Sponsor will be followed, in order to comply with GCP guidelines.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, e-mail, telephone, and fax).

Regulatory authorities, the IRB/IEC and other appropriate institutional regulatory bodies, and/or the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.7. Case Report Form Completion

CRFs will be completed for each study subject. It is the Principal Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Principal Investigator or designated representative, should complete the CRF screens as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Principal Investigator must sign and date the Investigator's Statement at the end of the CRF to endorse the recorded data.

8.8. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years following marketing application approval or 2 years after formal discontinuation of the clinical development of the

investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

The Sponsor has full rights over any invention, discovery, or innovation, patentable or not, that may occur when performing the study.

8.9. Liability Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

8.10. Publication and Presentation of Study Findings and Use of Information

All information regarding Elenagen Drug Product supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of Elenagen Drug Product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee comprised of Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication and presentation of the study results, which will reflect the experience of all participating clinical sites. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Sponsor and the investigator and/or the investigator's institution.

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