OX4325 (FOCUS): A Multicenter, Multinational, Double-blind, 2-Arm, Randomized, Phase 2/3, Study of Physician's Choice Chemotherapy (PCC) (Weekly Paclitaxel or Pegylated Liposomal Doxorubicin [PLD]) Plus Bevacizumab and CA4P Versus PCC Plus Bevacizumab and Placebo for Subjects with Platinum-Resistant, Recurrent, Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

NCT: NCT02641639

Protocol Amendment Date: 21 March 2017

1. SYNOPSIS

Name of Investigational Product:

CA4P

Name of Active Ingredient:

Fosbretabulin tromethamine, Combretastatin A4-Phosphate (CA4P)

Title of Study:

FOCUS: A Multicenter, Multinational, Double-blind, 2-Arm, Randomized, Phase 2/3, Study of Physician's Choice Chemotherapy (PCC) (Weekly Paclitaxel or Pegylated Liposomal Doxorubicin [PLD]) Plus Bevacizumab and CA4P Versus PCC Plus Bevacizumab and Placebo for Subjects with Platinum-Resistant, Recurrent, Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Studied period (months):	**Phase of development:**
Approximately 34 months (Part 1) and 46 months (Part 2)	Phases 2 (Part 1) and 3 (Part 2)

Objectives:

Part 1 will address the hypothesis that PCC plus bevacizumab and CA4P is a regimen worth investigating further in Part 2. Part 2 will further analyze the endpoints found to demonstrate the clinical benefit of PCC plus bevacizumab and CA4P in a larger study.

Primary:

- To demonstrate an improvement in progression-free survival (PFS) with the regimen of PCC plus bevacizumab and CA4P compared with PCC plus bevacizumab and placebo in subjects with platinum-resistant, recurrent, epithelial ovarian, fallopian tube or primary peritoneal cancer

Secondary:

- Improvement in objective response rate (ORR), using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and Gynecologic Cancer Intergroup (GCIG) cancer antigen-125 (CA-125) criteria
- Evaluation of overall survival (OS)
- Assessment of the proportion of subjects who remain progression-free at 6, 9, and 12 months on the regimen of PCC plus bevacizumab and CA4P compared with PCC plus bevacizumab and placebo
- To evaluate the safety and tolerability of PCC plus bevacizumab and CA4P versus PCC plus bevacizumab and placebo as measured by physical exams, vital signs, laboratory measures, electrocardiogram (ECG), Eastern Cooperative Oncology Group (ECOG) performance status (PS) and incidence of adverse events (AEs) using the National Cancer Institute (NCI)-Common Terminology Criteria for AEs (CTCAE) version 4.03.

Methodology:

This is a multicenter, multinational, randomized, double-blind, 2-arm, parallel-group, Phase 2/3 study to evaluate the efficacy and safety of PCC plus bevacizumab and CA4P versus PCC plus bevacizumab and placebo in subjects with platinum-resistant ovarian cancers (prOC). Subjects with platinum-resistant, recurrent, epithelial ovarian, primary peritoneal or fallopian tube cancer will be randomized 1:1 to receive PCC plus bevacizumab and CA4P or PCC plus bevacizumab and placebo. Subjects will be stratified by selected chemotherapy (PLD vs. paclitaxel), platinum free interval (< 3 vs. 3 to 6 months from last platinum therapy to subsequent progression), and line of therapy (2^{nd} vs. 3^{rd} / 4^{th}) (4^{th} line will be combined with 3^{rd} for this stratification moving forward). This is a 2-part study, consisting of a Phase 2, exploratory study (Part 1) followed by a Phase 3, pivotal study (Part 2). Parts 1 and 2 of this study will have a similar overall study design. Approximately 80 subjects will be randomized into Part 1 and approximately 356 subjects will be randomized into Part 2.

All subjects randomized will receive bevacizumab 10 mg/kg intravenously (IV) on Days 1 and 15, repeated every 4 weeks (q4wk) and PCC with paclitaxel 80 mg/m^2 IV on Days 1, 8, 15 and 22, repeated q4wk, or paclitaxel 80 mg/m^2 IV on Days 1, 8, 15, repeated q4wk or PLD 40 mg/m^2 IV on Day 1, repeated q4wk. Subjects in the Treatment Arm will also receive CA4P 60 mg/m^2 on the same day as bevacizumab (Days 1 and 15, repeated q4wk), while subjects in the Control Arm will receive placebo on those days.

Order of dosing will follow the guidance listed below during this study when bevacizumab and CA4P

/ Placebo are dosed the same day as PCC,

Bevacizumab followed by CA4P / Placebo followed after 1-3 hours by paclitaxel,

PLD followed by bevacizumab followed by CA4P / Placebo

Subjects will continue randomized treatment until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent, or sponsor discontinues study for any reason. Subjects will undergo tumor assessments (RECIST) during screening and every 8 weeks while on study and CA-125 levels during screening and every 4 weeks while on study.

The primary endpoint is PFS. Secondary endpoints include ORR, OS, proportion of subjects who remain progression free at 6, 9, and 12 months, and safety. Endpoints will be compared between the Treatment Arm and the Control arm. The study duration is estimated to last approximately 3 years for Part 1 with an additional approximately 4 years for Part 2.

This study will have 2 parts with the same overall design. Part 1 will enroll up to approximately 80 subjects and will include multiple interim analyses to test the safety and efficacy assumptions in this specific subject population. Upon meeting certain efficacy criteria in Part 1, the protocol will be amended and additional sites added in order to enroll an additional 356 subjects into Part 2 of the study. Subjects enrolled in Part 2 will be analyzed separately and used as a stand-alone confirmatory efficacy study.

Number of subjects (planned):

Part 1 will consist of approximately 80 subjects and Part 2 will consist of approximately 356 subjects.

[redacted]

Study Centers:

Approximately 50 sites are planned for Part 1 including sites in the US and EU. An additional number of sites will be added during Part 2 to support subject recruitment requirements.

Entry Criteria:

This study will treat subjects with platinum-resistant, recurrent, epithelial ovarian, fallopian tube or primary peritoneal cancer.

Inclusion:

1. Signed informed consent form (ICF)
2. Age ≥ 18 years (Age ≥ 19 years if required by local regulatory authorities)
3. ECOG PS of 0-1
4. Histologically or cytologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer in recurrent stage
5. prOC (platinum-resistant ovarian cancers) defined as progression within > 1 to < 6 months (+ 2 weeks) of completing previous cycle of primary platinum-based therapy, or during or within < 6 months (+ 2 weeks) of starting additional platinum based therapies
6. Received ≥ 1 but ≤ 3 prior platinum-based regimens
7. Measurable disease according to RECIST 1.1
8. Left ventricular ejection fraction (LVEF) greater than or equal to at least 45% at baseline assessment if subject is receiving PLD, and/or anthracycline is a concomitant medication
9. No evidence of active (progressing) brain metastasis. (Treated brain metastasis allowed with a posttreatment magnetic resonance imaging (MRI) or Computed Tomography (CT) of brain showing no active (progressing) brain metastasis). Treatment of brain metastasis may include surgery, radiosurgery (linear accelerator (LINAC), gamma knife), or whole brain irradiation. Surgery for brain metastasis must be > 8 weeks from study entry
10. Hemoglobin > 9 g/dl. Erythroid growth factors should not have been used in the 2 weeks prior to study entry. Red blood cell transfusions are permitted to maintain the hemoglobin level 9 g/dl
11. Adequate bone marrow function in the investigator's opinion
12. Adequate hepatic function defined by the following:
    - Total bilirubin < 2 x Upper Limit of Normal (ULN)
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 X ULN for the referenced lab (< 5 X ULN for subjects with liver metastases)
13. Adequate renal function defined by the following:

[redacted]

- Serum creatinine < 2 X ULN for the referenced lab

14. Subjects of childbearing potential must have a negative serum pregnancy test prior to study entry and must be practicing a highly effective form of contraception
15. At least 2 weeks since prior radiotherapy and has recovered from any Grade 3 toxicities
16. Life expectancy ≥ 12 weeks

Exclusion:

1. Subjects who have received prior CA4P therapy
2. Previously having failed treatment with bevacizumab combined with the intended PCC.
   - For clarity: Investigators should not select a bevacizumab + PCC combination for the FOCUS trial if the patient has previously failed that same regimen, however they may select a new PCC regimen to combine with bevacizumab. For example, a patient who failed bevacizumab + weekly paclitaxel would be allowed to enroll in FOCUS only if they are assigned to bevacizumab + PLD for the study.
3. Previous treatment with greater than three traditional chemotherapy treatment regimens
4. Untreated brain metastasis or leptomeningeal brain metastasis
5. Solid organ or bone marrow transplant
6. Primary platinum-refractory disease (defined as progression during dosing or within one (1) month of completing the last cycle of patients first platinum-containing regimen)
7. > Grade 2 peripheral neuropathy
8. Current thrombotic or hemorrhagic disorder/event or history of prior event within 6 months of start of Screening
9. History of prior cerebrovascular event, (including transient ischemic attack) within 6 months of start of Screening
10. Recent history (within 6 months of start of Screening) of angina pectoris, myocardial infarction (including non-Q wave MI), or NYHA Class III and IV congestive heart failure
11. History of torsade de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (<60 bpm), heart block (excluding 1st degree block, benign PR interval prolongation only), congenital long QT syndrome or new ST segment elevation or depression or new Q wave on ECG
12. Known uncontrolled HIV infection
13. Uncontrolled, clinically significant active infection
14. Serious non-healing wound, ulcer or bone fracture

15. Subjects with known hypersensitivity to any of the components of CA4P, paclitaxel, PLD, or bevacizumab (paclitaxel and PLD dependent on whether PI plans they will be dosed with that PCC)
16. Subjects who are currently or planning on receiving concurrent investigational therapy or who have received investigational therapy for any indication within 30 days of the first scheduled day of dosing
17. Subjects with any other intercurrent medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a subject's ability to provide informed consent, cooperate and participate in the study, or to interfere with the interpretation of the study results
18. Subjects with other invasive malignancies, with the exception of non-melanoma skin cancer, or with previous cancer treatment that contraindicates this protocol therapy within last 3 years
19. Prior radiation therapy to the pelvis or abdomen within 4 weeks of entry into the study
20. History of fistula, gastrointestinal (GI) perforation or intra-abdominal abscess, or invasive disease/metastases of the bowel which in the investigators opinion may increase the risk of GI perforation with bevacizumab treatment.
21. Uncontrolled hypertension (HTN)
    - Sustained BP greater than 150 mmHG SBP / 100 mmHG DBP
22. Uncontrolled elevated proteinuria levels in the investigator's opinion
23. Corrected QT interval ([QTc] Fridericia) > 480 ms
24. Significant vascular disease or recent peripheral arterial thrombosis
25. Subjects with active bleeding or pathologic conditions that carry high risk of bleeding
26. Subjects who are pregnant or lactating

Investigational product, dosage and mode of administration:

All subjects randomized to the Treatment Arm will receive bevacizumab 10 mg/kg IV and CA4P 60 mg/m^2 IV on Days 1 and 15 repeated q4wk (1 cycle = 28 days). All subjects will also receive PCC.

PCC consists of **one** of the following 3 standard chemotherapy regimens, based on physician preference:

- Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15 and 22, repeated q4wk,
- Paclitaxel 80 mg/m^2 IV on Days 1, 8, 15 repeated q4wk,
- PLD 40 mg/m^2 IV on Day 1, repeated q4wk.

Criteria for evaluation:

Efficacy:

The primary endpoint is PFS, defined as the time from the date of randomization until progressive disease (PD) or death from any cause. Tumor assessments, using RECIST 1.1

[redacted]

criteria, will be performed during screening and repeated every 8 weeks from dosing using the same assessment technique used at baseline (CT or magnetic resonance imaging [MRI]). Assessment of PFS will be based on the principal investigator's (PI's) or qualified individuals (thru experience or training) assessment, but scans will be collected for possible additional review.

Secondary endpoints include ORR, OS and the proportion of progression-free subjects at 6, 9 and 12 months. The ORR will be defined as the proportion of subjects with a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 criteria, based upon the best response. The ORR will be determined based on investigator assessment according to RECIST 1.1 criteria and/or GCIG CA-125 criteria. Overall survival is defined as the time from randomization to the date of death from any cause. The proportion of progression-free subjects at 6, 9 and 12 months will be based on the number of evaluable subjects at each time point who have not progressed per investigator or qualified individual assessment using RECIST 1.1.

Safety:

Safety and tolerability will be measured by physical exams, vital signs, laboratory measures, ECOG PS, and incidence of AEs using the NCI CTCAE version 4.03. Safety summaries will be reviewed by Data Safety Monitoring Committee (DSMC) during the defined interim analyses of Part 1, including analysis of certain AEs of Special Interest that will be outlined in the Statistical Analysis Plan. The DSMC will consist of Mateon employees and consultants with meetings post each interim analysis to review safety summaries and AEs of special interest data. An Independent Data Monitoring Committee (IDMC) will be established to review the safety data summaries and examine the findings of the interim futility analysis in Part 2. The IDMC will consist of an independent statistician and two independent physicians with meetings to review study safety summaries and analyze AEs of special interest data. Details on the review will be established in a DMC charter, to be completed prior to initiation of Part 2 of the study.

Statistical methods:

Primary Efficacy Variable:

PFS is the primary efficacy endpoint and is defined as the time from the date of randomization to disease progression or death from any cause. Subjects will be followed until their date of death, loss to follow-up, withdrawal of consent for further follow-up for survival, or final database closure.

Subjects who are lost-to-follow-up or are not known to have disease progression at the time of data- cut-off for analysis will be censored at last date shown to be alive. Subjects who do not have any follow up since randomization will be censored at the date of randomization.

The primary efficacy analysis of PFS will be based on the intent-to-treat (ITT) population, using a stratified 2-sided log-rank test to test the hypothesis of equality of the survival curves between groups

(0.05 significance level). Kaplan-Meier estimates of the survival curves and the median survival times and their corresponding 95% confidence interval (CI) will be presented by

treatment group. Cox's proportional hazards regression model will also be used to compare hazard rates between the 2 treatment groups, adjusting for selected chemotherapy (PLD vs. paclitaxel), platinum free interval (< 3 vs. 3 to 6 months from last platinum therapy to subsequent progression), and line of therapy (2^{nd} vs. 3^{rd} / 4^{th}). The hazard ratio (HR) and its 95% CI will be calculated.

The robustness of the principal analysis of PFS described above will be examined through sensitivity analyses that will be considered supportive to the principal analysis. The suggested sensitivity analysis only includes well-documented and verifiable progression events.

Subgroup analyses of PFS will be performed to assess whether the treatment effect is concordant among subgroups. The planned subgroup analyses are based on age categorization (ages < 40 years,

40- < 65 years, and ≥ 65 years), selected chemotherapy (PLD vs. paclitaxel), platinum free interval (< 3 vs. 3 to 6 months from last platinum therapy to subsequent progression), and line of therapy (2^{nd} vs. 3^{rd} / 4^{th}), ECOG status at baseline (0 vs. ≥ 1), race (White, Black, Asian, and other), and time from initial diagnosis to randomization (< 2 vs. ≥ 2 years).

Secondary Efficacy Variables:

The ORR will be assessed at each radiographic assessment by the investigator or qualified individual using the following criteria:

- By RECIST only ("RECIST Responders")
- By RECIST and CA-125 response criterion ("Responders")
- By CA-125 response criterion only ("CA-125 Responders")

The ORR will be defined as the proportion of subjects with a CR or a PR per RECIST based upon the best response as assessed; confirmation of response is not required.

The ORR will be analyzed using The Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors to assess the significance of the treatment effect on ORR. The treatment effect on ORR will be quantified using the odds ratio. Clopper-Pearson 2-sided 95%

confidence limits will be calculated for the proportion of subjects with ORR in each group.

The ORR analyses will be performed for the Efficacy Evaluable population. Subjects who do not have measurable disease at baseline will be excluded from the population.

In addition to representing ORR, the best response using response categories CR, PR, stable disease

(SD), progressive disease (PD), and not evaluable (NE) will be tabulated. The proportion of the response in each response category will be calculated. Subjects who do not have any post-baseline tumor assessment will be counted under the NE category.

Safety Variables:

The safety data will include AEs, serious adverse events (SAEs), ECOG PS, clinical laboratory tests, vital signs and physical examination results. Summaries will use the Safety Population and will be presented separately for subjects in the Treatment Arm and Control Arm. All

safety data will be presented in data listings. Adverse events will be coded by system organ class (SOC) and preferred term using MedDRA, version 18.1; severity will be based on NCI CTCAE Grade (version 4.03). A treatment emergent AE (TEAE) is defined as an AE that was not present prior to treatment with study drug, but appeared following treatment or was present at treatment initiation, but worsened during treatment. Incidence of TEAEs by MedDRA SOC, preferred term and relationship (Related/Not Related) to study drug will be summarized based on the safety population. Adverse event incidence rates will be summarized using frequency and percentage. Adverse event data will be descriptively evaluated by treatment arm and for overall subjects.

[redacted]

Interim Analysis and Data Monitoring:

This protocol will consist of a 2-part study design consisting of an exploratory study (Part 1) followed by a pivotal study (Part 2). Part 1 will include 4 exploratory interim analyses when approximately 20, 40, 60, and 80 subjects have completed 2 months of therapy. The final analysis of Part 1 will be conducted when PFS events are observed for 75% of the total 80 subjects. Data monitoring of PFS and/or ORR will continue until the data are sufficient to assess the response benefit of PCC plus bevacizumab and CA4P over the PCC plus bevacizumab and placebo. The sites, subjects, and investigators will be blinded to the data; the Sponsor will use the data to evaluate whether or not to continue to the pivotal portion (Part 2)

of the study. If proof of concept is achieved in Part 1, the study will continue to Part 2. Subjects in Part 1 will not be included in the Part 2 efficacy analysis, but will be followed for up to 10 months.

A futility interim analysis in Part 2 is planned when approximately 50% of PFS total events are observed. The total PFS events required is approximately 238.