

PAREXEL International

Laekna Limited

LAE002INT2001

An Open-Label Randomized Active-Controlled Phase II Clinical Study to Assess the Efficacy and Safety of afuresertib Plus Paclitaxel Versus Paclitaxel in Patients with Platinum-Resistant Ovarian Cancer

Statistical Analysis Plan

Version: 3.0

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	23 Jul 2020	New document for Final V1.0
2.0	10 Jan 2022	1. Update team member in signature page. 2. CSR SAP v2.0 had updated wording based on Protocol version 5.0. 3. General update: 1) Except for DM (Demographic) and DS (DISPOSITION), the other outputs won't be provided by overall column. 2) Change all 'Site data' to 'investigator data'. 3) Change the randomization factors to country, prior bevacizumab use, and number of prior platinum-based therapy. 4. Section 1: Update Protocol and eCRF version. 5. Section 3.1: 1) Change Figure 3.1 Study Schema based on Protocol version 5.0. 2) Change the randomization factors. 6. Section 3.2.2: Remove 'Eastern Cooperative Oncology Group (ECOG) performance status' from safety variables 7. Section 4.2.1: 1) Remove 'or on the day of' 2) change 'First' to 'Date of first' 8. Section 4.5: Delete Per-Protocol set and related summaries/content were deleted too. 9. Section 4.6: Remove 'mutation type' and change randomization stratification factors based on protocol amendment 5. 10. Section 4.7: 1) Change the section header to 'Prior and Concomitant Medication and Procedures' 2) Add 'A summary of prior anti-cancer therapy by anatomical therapeutic chemical subgroup (Level 4), WHO Drug base substance preferred name (Level 5), treatment group (Analysis set: FAS)' 11. Section 4.8: The treatment compliance summary and dose modification summary were deleted. 12. Section 4.8: 1) Remove 'relative dose intensity' related contents from section 4.8 due to it will be displayed in Section 4.10.1. 2) Add 'Compliance' for afuresertib. 13. Section 4.9.1: The null hypothesis was changed to two-sided, and the comparison is based on unstratified log-rank test with significant level at 0.05. 14. Section 4.9.1.2: Change randomization stratification factors based on protocol amendment 5. 15. Section 4.9.1.4: Updated some wording because OS will be tested after PFS becomes significant and alpha is protected

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		16. Section 4.9.1.5: Updated some wording based on Protocol 5.0, but the content does not change. 17. Section 4.9.2: 1) Add 'No post-baseline tumor assessment and no death' as a new censoring rule. 2) The PFS/OS/DOR will be performed by unstratified as primary analysis. The stratified method will be used as supporting analysis. 3) Remove 95% CI for 25th and 75th and add min/max for PFS summary. 4) To clarify the PFS will be evaluated on investigator assessments. 5) The 95% CI was removed from KM plot. 6) PP set for PFS analysis is deleted. 18. Section 4.9.3: 1) Add 'will be based on all FAS patients with measurable disease at baseline' to BOR/ORR/DCR to clarify that these responses should base on population with measurable disease at baseline. 2) PP set for BOR/ORR/DCR is deleted. 3) To clarify the ORR/DOR/DCR will be evaluated both investigator assessments and BICR data. 19. Section 4.9.3.2: Add general description for confirmed CR/PR. 20. Section 4.9.3.3: 1) Use wald method for treatment difference and Odds ratio and its CI. 2) The RR was removed. 21. Section 4.9.3.6: 1) Use wald method for treatment difference and Odds ratio and its CI. 2) The RR was removed. 3) Table 2 and related summary were removed 22. Section 4.10.1: 1) Remove 'dose intensity' from the summary. 2) Add 'Compliance' and its category to summary. 23. Section 4.10.2: 1) Separate all COVID-19 related table/listing into new outputs. 2) Delete "possibly related, probably related and definitely". 3) Updated all AE outputs sorting rule. 4) Update the sentence to "An overview of any AEs, TEAEs including severity, Drug related TEAEs including severity, serious TEAEs, TEAEs leading to withdrawals, TEAEs leading to drug interruption will be presented by treatment group." 24. Section 4.10.4: 1) "A by-patient listing of laboratory data will be provided including changes from baseline" was changed to "A by-patient listing of laboratory data will be provided". 2) By-visit summaries and change from baseline for laboratory were removed from analysis. 3) Only keep shift table of laboratory outputs in SAP. 4) Pregnancy test is deleted. 25. Section 4.10.5.1: 1) Remove "A summary of the absolute value and change from baseline in each vital sign
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		parameter by treatment group and time point." 2) "A by-subject listing of vital signs data will be provided including changes from baseline." was changed to "A by-subject listing of vital signs data will be provided." 26. Section 4.10.5.3: Remove "A summary of each ECG parameter at screening by treatment group." 27. Section 4.10.5.4: The ECOG section was deleted per Sponsor's comments. 28. Section 4.11.2: 1) Use forest plot for PFS/OS subgroup analysis. 2) Use the same method for ORR/DCR/CA-125 subgroup analysis. 29. Section 4.12: Update some wording based on protocol amendment 5. 30. APPENDIX 6-1: Updated the 'Time and Events Table' based on Protocol version 5.0. 31. Section 4.5.2: Remove "and had at least one valid post baseline safety assessment" from safety population definition. 32. Section 4.13: Added the difference between Protocol 5.0 and SAP.
3.0	18 Dec 2023	1. Section 1: Updated Protocol and CRF version. 2. SAP v3.0 had updated wording based on Protocol version 6.0. 3. Section 4.5.3: Updated PAS definition. 4. Section 4.5.4: Added PK evaluable set. 5. Section 4.6: (1) Added the description for 'duration of disease'. (2) Change from 'BRCA1/2 mutations' to 'BRCA mutations by NGS'. (3) Added 'duration of the PFI' to baseline characteristics summary. (4) Added "A summary of Eastern Cooperative Oncology Group (ECOG) performance status at baseline by treatment group and overall". (5) Added 'Existing conditions that preclude bevacizumab treatment' summary. (6) Changed to 'PI3K/AKT/PTEN pathway alterations by NGS' 6. Section 4.7: (1) Added the description for subjects who randomized but without study treatment taken. (2) Deleted 'Summary of the classifications of concomitant radiotherapy by treatment group'. (3) Changed the anatomical therapeutic chemical subgroup from level 4 to level 2. (4) Deleted 'Summary of prior anticancer therapy by anatomical therapeutic chemical subgroup (Level 4), WHO Drug base substance preferred name (Level 5), treatment group (Analysis set: FAS)' as it is duplicated. 7. Section 4.8 and Section 4.10.1: The analysis was summarized and listed based on safety set.

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		8. Section 4.9.1.6: Added stratification factors to the PFS/OS subgroup analysis. 9. Section 4.9.2: (1) Added 'and PFS rate at 6 months and 12 months' to PFS summary. (2) Added additional description for the patient died or PD after two missed consecutive TAs and without any post-baseline TAs. (3) Added additional description for the patient who started anticancer before death, but without any post-baseline TAs should be censored at randomization date. 10. Section 4.9.2, Section 4.9.3.1 and Appendix 6-2: Added imputation rule for death date. 11. Section 4.9.3.2: Updated to "To be assigned a status of SD, ~ after randomization at a minimum interval of 42 days." 12. Section 4.10.1: Updated the algorithm for Number of Planned Paclitaxel Injections. 13. Section 4.10.5: Removed 'ECOG performance status' from the description. 14. Section 4.10.5.2: Removed 'A summary of the number and percentage of subjects with normal/abnormal physical examination findings, by body system, treatment group and time point'. 15. Section 4.11.1.1: (1) Added geometric parameters for PK concentration summary. (2) Added Spaghetti plots. (3) Fixed the typo - PAS. 16. Section 4.11.1.2: (1) PK parameter analysis will be based on the PK evaluable set. (2) Updated the format of PK parameter. (3) Added geometric parameters for PK parameter summary. (4) Added 'Tlast'. (5) For AUC0-inf, added additional description "PK parameters AUC0-inf, t1/2, CL, CLss, CL/F, CLss/F, Vz, Vz,ss, Vz/F, Vz,ss/F, and Vss will not be included in the statistical summary". 17. Section 4.11.1.3: (1) Updated to "If n is less than 3, only n, minimum, and maximum will be reported.". (2) Updated reporting rule for geometric SD and geometric CV%. 18. Section 4.11.2: Changed to 'PI3K/AKT/PTEN pathway alterations by NGS' and 'BRCA mutations by NGS'. 19. Section 4.13: Removed the items that consistent with protocol 6.0. 20. LIST OF ABBREVIATIONS: Added 'NGS'. 21. Appendix 6-2: Added imputation rule for partial and missing dates of death.
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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical therapeutic chemical
AUC _τ	Area under the curve in the inter-dose interval period after first dose
AUC _{τ,ss}	Area under the curve in the inter-dose interval period at steady state
AUC ₀₋₂₄	Area under the curve from time 0 to 24 hours
BICR	Blinded Independent Central Review
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
BMI	Body Mass Index
BP	Blood pressure
BSA	Body Surface Area
CI	Confidence interval
C _{max}	Maximum concentration (after first dose)
C _{max,ss}	Maximum concentration at steady state
CR	Complete response
CRF	Case Report Form
C _{trough,ss}	Trough concentration at steady state
CV	Coefficient of variation
DBP	Diastolic blood pressure
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DRM	Data Review Meeting
ECG	Electrocardiogram

Abbreviation / Acronym	Definition / Expansion
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCIG	Gynecological Cancer Intergroup
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International normalized ratio
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not available
NAE	Not all evaluated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NK	Not known
NGS	Next generation sequencing
OC	Ovarian cancer
ORR	Overall response rate
OS	Overall survival
PARP	Poly ADP ribose polymerase
PD	Progressive disease
PFS	Progression-Free Survival
PR	Partial response

Abbreviation / Acronym	Definition / Expansion
PROC	Platinum-resistant ovarian cancer
PK	Pharmacokinetic(s)
PT	Preferred Term
SAE	Serious adverse event
SBP	Systolic blood pressure
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

This is an open-label randomized active-controlled phase II clinical Study to assess the efficacy and safety of afuresertib Plus Paclitaxel versus Paclitaxel in patients with platinum-resistant ovarian cancer (PROC). There are no clinical data for the combinations of afuresertib plus weekly paclitaxel in patients with PROC, especially in those who failed 1 to 5 prior platinum-based therapies, may or may not have been treated with bevacizumab previously. It is critical to understand the safety and anticancer efficacy of the afuresertib plus weekly paclitaxel combination. The main purpose of this study is to evaluate the safety and efficacy of this combination of afuresertib plus weekly paclitaxel versus weekly paclitaxel alone in patients with PROC. This study may be used for registration purposes with regulatory agencies.

This Statistical Analysis Plan (SAP) describes the detailed statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for Tables, Listings and Figures (TLF). It includes the variables and analysis dataset, and manipulations as well as other types of analyses that was not mentioned in the protocol.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 6.0 (January 23, 2023) (September 20, 2021)
- Electronic Case Report Form (eCRF), version 14.0 (November 30, 2023)

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

- To evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in patients with PROC.

2.2 Secondary Objective(s)

- To further evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel in patients with PROC.
- To characterize the pharmacokinetics (PK) of afuresertib and paclitaxel in patients with PROC under combination therapy of afuresertib plus paclitaxel, or paclitaxel alone at steady-state.
- To explore potential effect of coadministration of afuresertib on the PK of paclitaxel at steady state using paclitaxel alone as the mono control.
- To evaluate the safety and tolerability of afuresertib plus weekly paclitaxel or weekly paclitaxel in patients with PROC.

2.3 Exploratory Objective(s)

- To explore the efficacy of the combination treatment group versus paclitaxel arm in association with the following biomarkers:
 - Alterations of PI3K/AKT/PTEN pathway and BRCA1/2 mutations in tumor samples as assessed by next generation sequencing (NGS)

- Levels of phospho-AKT in tumor sample as assessed by immunohistochemistry (IHC)
- To perform Population PK (PopPK) modelling for afuresertib to characterize afuresertib PK and assess potential effect of coadministration of paclitaxel on the PK of afuresertib

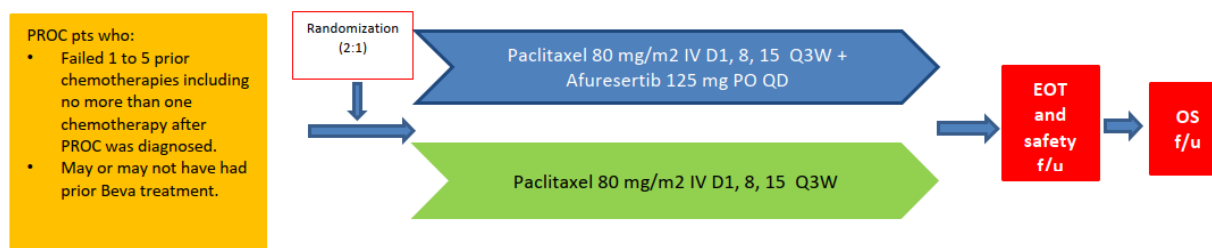
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is an open-label randomized active-controlled phase II clinical Study to assess the efficacy and safety of afuresertib Plus Paclitaxel versus Paclitaxel in patients with platinum-resistant ovarian cancer.

The study will consist of 3 periods. Screening Period (Day -24 to -1), Treatment Evaluation Period with a randomized, open-label, two-arm parallel, Follow-up Period. See the study schema [Figure 3-1](#) and time and events table [Appendix 6-1](#).

Figure 3-1. Study Schema



D = Day; EOT = End of treatment; f/u = Follow-up; OS = Overall survival; PARPi = Poly ADP ribose polymerase inhibitor; PD: Progressive disease; PO = Per os (oral); PROC = Platinum-resistant ovarian cancer; Q3W = Once every 3 weeks; QD = Once daily.

EOT visit and safety follow-up: within 30 days ($\pm$ 7 days) of last dose.

OS follow-up: every 12 weeks ($\pm$ 7 days) continuing after EOT.

The afuresertib plus paclitaxel combination therapy arm starts from the first day (Day 1) after randomization. The PK study will be performed in both the afuresertib plus paclitaxel arm and paclitaxel alone arm.

A total of approximately 141 patients with PROC are planned to be enrolled and randomized with a 2:1 ratio in an open-label manner to the 2 arms (94 patients in the combination treatment arm and 47 patients in the paclitaxel arm) for efficacy and safety evaluation. The randomization will be stratified by country: the United States vs China, prior bevacizumab use (yes vs. no) and number of prior platinum-based therapy treatments (1-2 versus 3-5 prior platinum regimens).

Patients will be randomized into two parallel open-label arms:

- Arm 1 is afuresertib 125 mg PO QD + paclitaxel 80 mg/m² intravenous (IV) infusion in 1 hour on Day 1, 8 and 15 of a 3-week cycle
- Arm 2 is paclitaxel 80 mg/m² IV infusion in 1 hour on Day 1, 8, and 15 of a 3-week cycle

Patients must have had 1 to 5 prior platinum-based chemotherapy regimens including no more than one chemotherapy after PROC was diagnosed. Combination therapy will be considered as one treatment, whereas maintenance therapy will be considered as the continuation of previous systemic treatment, such as PARP inhibitor or bevacizumab, are considered as the maintenance

therapy. In addition, patient's OC must have relapsed between 1 to 6 months after the last dose of the first-line platinum-based therapy (at least 3 cycles), or progress during or relapsed within 6 months of the last dose of platinum-based 2nd-5th line therapies. Based on the investigator's clinical judgement, all enrolled PROC patients in this study should be appropriate candidates for use of weekly paclitaxel for treatment of PROC.

3.2 Endpoints

3.2.1 Efficacy Variables

The primary efficacy endpoint of this study is progression-free survival (PFS) which is defined as the time from random assignment in a clinical trial to disease progression or death due to any reason based on RECIST 1.1^[1].

The secondary efficacy variables to further evaluate the clinical efficacy of afuresertib plus weekly paclitaxel versus weekly paclitaxel are:

- Overall survival (OS)
- Objective response rate (ORR) according to RECIST 1.1
- Duration of response (DOR) according to RECIST 1.1
- Disease control rate (DCR) according to RECIST 1.1
- Best overall response (BOR) according to RECIST 1.1
- Cancer antigen-125 (CA-125) response (Gynecological Cancer Intergroup [GCIG ^[2]])

PK of afuresertib and paclitaxel in patients with PROC when administered as the combination therapy by evaluating relevant PK parameters including but not limited to:

- Area under the curve in the inter-dose interval period after first dose (AUC_{τ}) and at steady state ($AUC_{\tau_{ss}}$)
- Maximum concentration after first dose (C_{max}) and at steady state ($C_{max_{ss}}$)
- Time to maximum concentration after first dose (T_{max}) and at steady state ($T_{max_{ss}}$)
- Half-life ($T_{1/2}$) if data permit
- Trough concentration at steady state ($C_{trough_{ss}}$)

3.2.2 Safety Variables

Safety assessment will include adverse event (AE), pregnancy test, physical examinations, vital signs, 12-lead electrocardiogram (ECG), laboratory tests and tolerability of study drug. The timing of all such assessments could be referred to [Appendix 6-1](#).

3.3 Exploratory Variables

Exploratory variables to explore the efficacy of the combination treatment group versus paclitaxel arm in the biomarker-defined subpopulations are:

- PFS based on RECIST 1.1
- OS
- ORR based on RECIST 1.1
- BOR based on RECIST 1.1
- DOR based on RECIST 1.1

- DCR based on RECIST 1.1
- CA-125 response (GCIG)

4 STATISTICAL METHODS

4.1 Data Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Laekna Limited or its designee may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventive actions to address any findings/issues identified.

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, 25th and 75th percentiles will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator if otherwise specify. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as “<0.001”.

Confidence intervals will be presented to one more decimal place than the raw data.

4.2.1 Baseline and Study Day

Unless otherwise specified, ‘Baseline’ assessments are defined as the last available assessments performed prior to first administration of trial medication. Study Day will be calculated relative to the date of first study treatment, as follows, and will be displayed in some of the patient listings.

- Study Day = Assessment Date – Date of first study treatment for visit (or event) prior to first study treatment.
- Study Day = Assessment Date – Date of first study treatment + 1 for visit (or event) at or after first study treatment.

4.2.2 Analysis Visit Window

For by-visit summaries, data will be analyzed by nominal visit based on the eCRF. Analyses will not exclude patient data due to the patient's failure to comply with the scheduled visit window as defined in [Appendix 6-1](#). If there is more than one assessment within a scheduled visit window, if otherwise specified, the assessment at the nearest date to the planned visit date will be prioritized, if the distances of two or more assessments to the planned visit date are the same, the assessment at the latest date will be prioritized.

For across visit summaries (e.g. maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

4.3 Software

All report outputs will be produced using SAS[®] version 9.3 or a later version in a secure and validated environment.

PK analyses will be produced using WinNonLin version 8.0 or a later version in a secure and validated environment.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- A summary of the number of subjects screened for entry into the study and the number and percentage of subjects excluded prior to randomization by major reason and overall (Analysis set: All Subjects)
- A summary of the number of subjects randomized, the number and percentage of subjects treated (with at least one dose of study treatment), the number and percentage of subjects withdrawing from study treatment and withdrawing from the study by treatment group and overall. Subjects withdrawing from the study and from study treatment will also be summarized by major reason. Subjects withdrawing from study and from study treatment related to COVID-19 will also be summarized (Analysis set: FAS).

By-patient listings of eligibility details, randomization details and withdrawal/trial completion details (including reason for discontinuation, dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each subject) will be provided.

4.4.2 Protocol Deviations

Protocol deviations include those deviations from the protocol that will be assessed as “Major” or “Minor” in collaboration with Sponsor.

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject’s rights, safety, well-being, and/or on the validity of the data for analysis.

Major COVID-19 protocol deviations are defined as those deviations result of COVID-19 that are likely to have an impact on the subject’s rights, safety, well-being, and/or on the validity of the data for analysis.

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Deviations will be defined on a Data Review Meeting (DRM) shortly prior to the final database lock. Results and population assignments will be summarized in a DRM report which will be signed off by all relevant scientific experts.

The following summary will be provided:

- A summary of the number and percentage of subjects with a major protocol deviation by treatment group and by type of deviation (Analysis set: FAS)
- A summary of the number and percentage of subjects with a major COVID-19 protocol deviation by treatment group and by type of deviation (Analysis set: FAS)

A by-subject listing of major/minor protocol deviations will be provided.

4.5 Analysis Sets

Analysis populations will be defined for efficacy and safety/PK data analysis. Analysis populations defined in this trial includes Full Analysis Set (FAS), Safety Set (SS), and PK Analysis Set (PAS). They will be derived logically based on the defined criteria and the result of protocol deviation review process, in which all potential protocol deviations will be assessed for the impacts to data analysis and will be judged how to handle the data.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to Laekna Limited for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to final database lock and will be documented and approved by Laekna Limited.

The analysis population will be summarized as follows:

- A summary of the number and percentage of patients included for each analysis population by treatment group (Analysis set: FAS)

A by-patient listing of analysis population details will be provided. This listing will be presented by treatment group and will include: center, subject identifier, inclusion/exclusion flag for each population and reason for exclusion from each population.

4.5.1 Full Analysis Set

The **Full Analysis Set (FAS)** comprises all patients who were randomized and assigned to a study treatment. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

If a subject is allocated the incorrect study treatment as per the study randomization list, subjects will be summarized and analyzed 'as randomized', i.e. by the randomized treatment group.

4.5.2 Safety Set

The **Safety Set (SS)** includes all patients from the FAS who have received at least one dose of study treatment. Safety Set will be used for all safety analyses.

If a subject is allocated the incorrect study treatment as per the study randomization list, subjects will be summarized and analyzed 'as treated', i.e. by the allocated treatment group. The treatment group 'as treated' will be widely discussed, decided and documented in DRM if subject is allocated the incorrect study treatment at some time of study treatment.

4.5.3 PK Analysis Set

The **PK Analysis Set (PAS)** consists of all patients who have received at least one dose of the IP and who have at least one sample providing quantifiable concentration value after drug administration at the scheduled PK timepoint. All patients in PAS will be analysis by the allocated treatment and analyte.

Mean, Spaghetti and individual plasma concentrations plots will be produced on both the linear /linear scale and the log₁₀/linear scale for the PAS.

4.5.4 PK Evaluable Set

The **PK Evaluable Set** consists of all patients who have sufficient evaluable concentration-time profile to allow determination of at least one PK parameter. An evaluable concentration-time profile will be determined at the discretion of the Pharmacokineticist following examination of subjects with dosing.

Summary statistics of PK concentration (number of subjects with an observation, arithmetic mean, SD, arithmetic CV%, median, minimum, maximum, geometric mean, geometric SD and geometric CV%) will be calculated for each time point in plasma for the PAS.

Summary statistics of PK parameters in plasma (number of subjects, arithmetic mean, SD, arithmetic CV%, median, minimum, maximum, geometric mean, geometric SD and geometric CV%) will be calculated for the PK Evaluable Set.

4.6 Demographic and Other Baseline Characteristics

Subject demographic and other baseline characteristic including disease characteristics will be summarized descriptively based upon the FAS population. The following demographics and baseline characteristics and stratification factors (With exception of site) will be summarized:

- A summary of demographic variables (age, sex, race, Ethnicity, height, weight, BMI and BSA) by treatment group and overall.

- A summary of baseline disease status, including but not limited to metastases (Yes or No), duration of disease (years, from first ovarian cancer diagnosis date to randomization), histological type by treatment group and overall.

Duration of disease will be calculated as (Date of randomization - First ovarian cancer diagnosis date + 1)/365.25. If first ovarian cancer diagnosis date is partial date with missing day only will be assumed to be 1st of the month, and partial dates with both missing day and month will be assumed to be January 01.

- A summary of stratification factors, including country (the United States vs. China), prior bevacizumab use (yes vs. no) and existing conditions that preclude bevacizumab treatment, and number of prior platinum-based therapy treatments (1-2 vs. 3-5 prior platinum regimens) by treatment group and overall.
- A summary of medical history by treatment group.
- A summary of biomarker at baseline for phosphoinositide 3 kinase (PI3K)/AKT/PTEN pathway alterations by NGS, BRCA mutations by NGS and/or level of phospho-AKT by IHC, and duration of the platinum free interval (PFI) (1-3 months vs >3-6 months) by treatment group and overall.
- A summary of Eastern Cooperative Oncology Group (ECOG) performance status at baseline by treatment group and overall.

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent. Age is collected in eCRF with the following rules:

Compute the difference in years between date of birth (DOB) and date of inform consent.

If the month of inform consent is earlier than the month of DOB or if the month is the same but the day of consent is earlier than the day of DOB, then subtract 1 year from the calculated age.

If DOB is partial date (missing day and month), age will be derived as (year of inform consent) – (year of birth) – 1, to apply conservative age for unknown day and month cases.

BMI (kg/m²) derived as $weight(kg)/height(m)^2$.

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by System Organ Class (SOC) and Preferred Term (PT).

By-patient listings of demographic data and other baseline characteristics (as summarized above) will be provided.

4.7 Prior and Concomitant Medication and Procedures

All medications and procedures, including radiotherapy, anti-cancer medical therapy, anticancer surgery or procedures during the study will be summarized and listed. Medications will be coded by latest World Health Organization Drug Dictionary (WHODD) version, and therapies will be coded by latest MedDRA version.

Medication collected in eCRF “Prior and Concomitant Medication” will be classified as Prior only if start and stop prior to the date of first dose of study treatment. If a medication starts before the date of first dose of study treatment and stops on or after the date of first dose of study treatment, then the medication will be classified as both Prior and Concomitant. Medications will be classified

as Concomitant only if they have a start date on or after the date of first dose of study treatment and no more than 30 days after last administration of any trial medication component.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study treatment. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study treatment. If there is clear evidence to suggest that the medication started prior to the first dose of study treatment, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study treatment. If there is clear evidence to suggest that the medication stopped prior to the first dose of study treatment, the medication will be assumed to be Prior only.

For subjects who have been randomized but not treated with any study treatment, the randomization date will be used as the reference date for medication classification.

Incomplete dates of medication will be imputed as detailed in [Appendix 6-2](#): Imputation algorithm for partial and missing dates.

The following summary will be provided:

- A summary of prior medication other than for anti-cancer therapy by anatomical therapeutic chemical subgroup (Level 2), WHO Drug base substance preferred name (Level 5), treatment group (Analysis set: FAS)
- A summary of prior anti-cancer therapy by anatomical therapeutic chemical subgroup (Level 2), WHO Drug base substance preferred name (Level 5), treatment group (Analysis set: FAS)
- A summary of concomitant medication by anatomical therapeutic chemical subgroup (Level 2), WHO Drug base substance preferred name (Level 5), treatment group (Analysis set: FAS)
- Summary of the classifications of prior radiotherapy by treatment group (Analysis set: FAS)
- Summary of the classifications of concomitant procedures by treatment group (Analysis set: FAS)
- Summary of prior disease related surgery by SOC, preferred term, treatment group. (Analysis set: FAS)

By-subject listings of medication, surgery, therapy, radiotherapy will be provided respectively.

4.8 Treatment Compliance

Relative dose intensity and compliance will be summarized for the study to assess tolerability and oral drug compliance respectively.

The relative dose intensity will be calculated for afuresertib and Paclitaxel respectively. The compliance will be calculated for afuresertib only. For the definition of relative dose intensity and summary of each please refer to [Section 4.10.1](#).

The compliance of afuresertib is defined as:

- Compliance = [Total cumulative actual dose in CRF [mg] / Sum of (duration of prescribed treatment × physician prescribed dose)].

A by-subject listing of treatment compliance will be provided for Safety Set.

4.9 Efficacy Evaluation

4.9.1 Analysis and Data Conventions

This study is designed to test for superiority. The null hypothesis for the treatment comparison will be that median PFS of Arm 1 (afuresertib + paclitaxel) is equal to that of Arm 2 (paclitaxel). The alternative hypothesis will be that PFS of Arm 1 (afuresertib + paclitaxel) is not equal to that of Arm 2 (paclitaxel). Symbolically, this is expressed as follows:

$$H_0: PFS_{\text{comb}} = PFS_{\text{ctrl}}$$

$$H_a: PFS_{\text{comb}} \neq PFS_{\text{ctrl}}.$$

The comparison of PFS between the two arms will be performed by a two-sided unstratified log-rank test with significant level at 0.05.

4.9.1.1 Multi-center Studies

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

4.9.1.2 Adjustments for Covariates

Sensitivity analysis of efficacy endpoints will be stratified by prior bevacizumab use and number of prior platinum-based therapy treatments.

- Prior bevacizumab use: yes versus no
- Number of prior platinum-based therapy treatments: 1-2 versus 3-5 prior platinum regimens

No adjustments will be made for covariates.

4.9.1.3 Handling of Dropouts or Missing Data

No imputation of missing data will be performed unless specifically stated.

4.9.1.4 Multiple Comparisons/Multiplicity

One primary variable has been defined for this study, with one critical treatment contrast Arm 1 versus Arm 2. The confirmatory testing of OS will only start if the null hypothesis for the PFS has been rejected and alpha is protected at two-sided 0.05 level for the study. The other secondary variables defined are intended to provide supportive evidence relating to the primary objective, no confirmatory testing of other secondary variables will be conducted.

4.9.1.5 Interim Analyses

No formal interim analyses are planned for the primary endpoint (PFS) of this study. The interim analysis of OS will be performed by the time of primary data analysis. The primary data analysis

(including interim analysis of OS) will be conducted when 105 events of PFS are observed. It is recognized that at that time, not all efficacy endpoints like OS will be mature; however, all efficacy and safety endpoints will be analyzed for this primary analysis. Hypothesis testing of OS will be conducted if improvement of PFS demonstrates statistical significance (for more multiplicity handling, See Section [4.9.3.1](#)).

4.9.1.6 Examination of Subgroups

Subgroup analyses will be performed to evaluate the efficacy of afuresertib administered in combination with paclitaxel versus paclitaxel in biomarker-defined subpopulations. Please refer to Section [4.11.2](#) for details. The PFS and OS will be also examined for the following subgroups:

- Country (United States versus China)
- Prior bevacizumab use (no versus yes)
- Number of prior platinum-based therapy treatments (1-2 versus 3-5 prior platinum regimens)
- Duration of the PFI (1-3 months versus >3-6 months)

4.9.2 Primary Efficacy Variable

The primary efficacy endpoint of this study is PFS which is defined as the time from random assignment to disease progression or death (whichever occurs first) based on RECIST 1.1 as assessed by investigator.

The unit of PFS will be month, which equals to the Duration in Days /30.4375.

Incomplete dates of death will be imputed as detailed in [Appendix 6-2](#): Imputation algorithm for partial and missing dates.

The PFS will be censored based on the following algorithms:

- Subjects without baseline tumor assessment will be censored at date of randomization.
- Subjects without post-baseline tumor assessment and no death will be censored at date of randomization.
- Subjects without PD or death will be censored at the date of last effective tumor assessment.
- Subjects who started anticancer treatment before reporting PD or death will be censored at the date of the final evaluable tumor assessment prior to the start of the subsequent anticancer therapy. If the subject does not have post-baseline tumor assessment and start anticancer treatment before reporting PD or death, they will be censored at date of randomization.
- Subjects have PD or death after two or more missed consecutive scheduled tumor assessments will be censored at the date of the last evaluable tumor assessment prior to PD or death. If the subject does not have post-baseline tumor assessment or does not have baseline tumor assessment, they will be censored at date of randomization unless they have PD or death within two consecutive tumor assessments of randomization (12 weeks + 7 days allowing for a late assessment within the post-baseline tumor assessments visit window).

Refer to **Table 1** for the rules for determining PFS event or censoring date.

Table 1 Rules for determining PFS event or censoring date

Rule #	Situation	Outcome	Date of PFS event or censoring
1	No baseline tumor assessment	censored	Date of randomization
2	No post-baseline tumor assessment and no death	censored	Date of randomization
3	Progression documented on or between scheduled visits	event	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions) • Date of last radiological assessments of non-target lesions (if progression is based on non-target lesions)
4	No progression and no death	censored	Date of last radiological assessment
5	New anticancer treatment started without documented PD or death	censored	Date of last radiological assessment before initiation of anticancer treatment
6	Death before first PD assessment	event	Date of death
7	Death between adequate assessment visits	event	Date of death
8	Death or progression after two or more missed visit	censored	Date of last radiological assessment before PD or death

The comparison of PFS between the two arms will be performed by unstratified log-rank test. Median PFS and PFS curve will be estimated using Kaplan-Meier method. The Brookmeyer-Crowley method will be used to construct the 95% CI for the median PFS. The standard error of the Kaplan-Meier quartile estimates will be estimated using Greenwood's formula. The hazard ratio and its 95% CI will be estimated by unstratified Cox proportional hazards model using treatment group as fixed effect. Efron's method will be used to handle ties.

The primary efficacy endpoint will be analyzed using stratified log-rank test with the stratification factors (With exception of country) at randomization: prior bevacizumab use (yes vs. no) and number of prior platinum based therapy treatments (1-2 versus 3-5 prior platinum regimens) as a supporting analysis. The hazard ratio and its 95% CI will be also estimated by stratified Cox proportional hazards model using the same stratification factors.

The following summary will be provided for primary analysis and supporting analysis:

- A summary of PFS events and censored number with different reasons by study treatment group (Analysis set: FAS)
- A summary of the PFS including the median PFS with corresponding 95% CI if it is evaluable, the quartile PFS, minimum, and maximum by study treatment group, together with the hazard ratio and its 95% CI, and PFS rate at 6 months and 12 months (Analysis set: FAS)
- A plot of Kaplan-Meier survival curve by study treatment group (Analysis set: FAS)

In addition, following sensitivity analysis will be performed:

- Repeat the primary analysis using the BICR-reviewed tumor assessment. The definition of event and censor date are same as primary analysis. (Analysis set: FAS)
- Repeat the primary analysis using tumor assessment based on RECIST 1.1, but death or progression after two or more missed visit will be analyzed as event rather than censor. (Analysis set: FAS)
- Repeat the primary analysis using tumor assessment based on RECIST 1.1, but new anticancer treatment started without documented PD or death will be analyzed as event rather than censor. (Analysis set: FAS)

A by-subject listing of the primary efficacy data will be provided.

4.9.3 Secondary Efficacy Variables

4.9.3.1 Overall survival (OS)

OS is defined as the time from randomization until death for any reason. Subjects who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

Incomplete dates of death will be imputed as detailed in [Appendix 6-2](#): Imputation algorithm for partial and missing dates.

Statistical methods are the same as those for the primary efficacy endpoint (Analysis set: FAS). Although the study is not powered for the secondary endpoint OS, two-sided unstratified log-rank test will be performed to test the difference of OS between the two treatment arms if improvement of PFS has been demonstrated with statistical significance (i.e. null hypothesis of PFS has been rejected).

The testing will be conducted at the time of primary data analysis and the end of study, which is defined as the time when 105 patients died for any reason. The significance level of two-sided 0.05 is considered. The O'Brien-Fleming type Lan- Demets alpha-spending function will be applied for adjustment of the significance levels in the interim and final analyses to control the type I error. The actual alpha level for the interim and final analysis for OS will be calculated based on the actual number of events considered for the interim analysis.

4.9.3.2 Best overall response (BOR) according to RECIST 1.1

BOR calculated based on the overall visit responses from each RECIST assessment and all FAS patients with measurable disease at baseline. It is the best response a subject has had from randomization until RECIST progression or the last evaluable assessment in the absence of RECIST progression. BOR will be evaluated based on both investigator data and BICR data

respectively (will only be evaluated based on investigator data if BICR assessment is finally not applicable for the study).

Categorization of BOR will be based on the RECIST 1.1 criteria using the following response categories: CR, PR, stable disease (SD), progressive disease (PD) and not evaluable (NE) (CR>PR>SD>PD>NE).

To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after randomization at a minimum interval of 42 days. If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative patients lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered NE.

For subjects whose progression event is death, BOR will be calculated based on data up until the last evaluable RECIST assessment prior to death. If no evaluable RECIST assessments prior to death, then BOR will be assigned as PD.

Progression events that have been censored due to them being more than two missed visits or new anticancer treatment started after the last evaluable assessment will not contribute to the BOR derivation.

CR/PR should be confirmed based on RECIST 1.1 and the minimum interval between two assessments should be no less than 28 days.

A summary of BOR according to RECIST 1.1 by treatment group will be provided. (Analysis set: FAS)

4.9.3.3 Objective response rate (ORR) according to RECIST 1.1

ORR defined as percentage of subjects with a best overall response of CR or PR according to RECIST 1.1 and will be based on all FAS patients with measurable disease at baseline. ORR will be evaluated based on both investigator data and BICR data respectively (will only be evaluated based on investigator data if BICR assessment is finally not applicable for the study).

The Clopper-Pearson method will be used to provide an estimation of ORR with 95% CIs for each treatment group. The risk difference ($ORR_{comb} - ORR_{ctrl}$) and odds ratio ($\frac{ORR_{comb}(1-ORR_{ctrl})}{ORR_{ctrl}(1-ORR_{comb})}$) and their 95% CIs will be presented as well, using Wald approach.

4.9.3.4 Duration of response (DOR) according to RECIST 1.1

DOR is defined as time from first observation of response (CR or PR) until first observation of documented disease progression or death according to RECIST 1.1, whichever occurs first, in subset of subjects with best overall response CR or PR. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a patient does not progress following a response, then his/her DOR will use the PFS censoring time. DOR will be evaluated based on investigator data and BICR data respectively (will only be evaluated based on investigator data if BICR assessment is finally not applicable for the study).

Duration of response will not be defined for those subjects who do not have a documented response. Statistical methods are the same as those for the primary efficacy endpoint (Analysis set: FAS).

4.9.3.5 Disease control rate (DCR) according to RECIST 1.1

DCR is defined as the percentage of subjects with the best overall response of CR, PR or SD to study treatment according to RECIST 1.1 and will be based on all FAS patients with measurable disease at baseline. DCR will be evaluated based on both investigator data and BICR data respectively (will only be evaluated based on investigator data if BICR assessment is finally not applicable for the study).

Statistical methods are the same as those for ORR.

4.9.3.6 Cancer antigen-125 (CA-125) response

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening CA-125 values and the 28-day confirmatory value must be less than or equal to (within an assay variability of 10%) the previous values.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies, medical or surgical manipulation of the peritoneum or pleura during the previous 28 days.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. FAS set will be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responders. Patients who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range have not had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

Same as ORR, following analysis will be provided for CA-125 response rate and CA-125 complete response rate:

The Clopper-Pearson method will be used to provide an estimation of CA-125 response (or complete response) rate with 95% CIs for each treatment group. The risk difference and odds ratio and their 95% CIs will also be presented by Wald approach.

4.10 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in [Section 4.5](#) unless otherwise specified.

4.10.1 Extent of Exposure

Total exposure duration is defined as date of last dose minus date of first dose + 1, regardless of any intermittent interruptions.

Dose intensity = Actual dose received / Actual duration;

Planned Dose intensity = Planned dose received / Planned duration.

Planned dose intensity for afuresertib = 125 mg/day.

The actual duration and planned duration are same for overall study treatment period. Therefore:

Planned dose intensity for paclitaxel = $80 \text{ mg/m}^2 \times \text{number of planned paclitaxel injections} / (\text{last date of paclitaxel} - \text{first date of paclitaxel} + 1)$.

Number of planned paclitaxel injections = [Nearest integer part of (last date of paclitaxel – first date of paclitaxel)/7] + 1. So, if the 1st injection is 1st January, and the last injection is 9 January, then the number of planned injections would be ([Nearest integer part of 8/7] + 1 = 2), if the 1st injection is 1st January, and the last injection is 27 January, then the number of planned injections would be ([Nearest integer part of 26/7] + 1 = 5).

Actual dose intensity for paclitaxel = Sum of actual dose level for paclitaxel [mg/m^2] / (last date of paclitaxel – first date of paclitaxel + 1).

Actual dose level for paclitaxel [mg/m^2] = Actual total dose infused in CRF [mg] / (Expected Dose to be administered in CRF [mg] / Dose level in CRF [mg/m^2]).

Relative dose intensity = Dose intensity / Planned Dose intensity.

The actual dose, duration in days of study treatment, relative dose intensity, and compliance for afuresertib will be listed and summarized by means of descriptive statistics.

Categories for relative dose intensity and compliance of study drug will be specified as < 0.5 , ≥ 0.5 - < 0.75 , ≥ 0.75 - < 0.9 , ≥ 0.9 - < 1.1 and ≥ 1.1 . The number and proportion of patients within each category will be presented by treatment within each arm. The Safety Set will be used.

4.10.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version x.x or higher.

Treatment-emergent adverse events will be tabulated and are defined as those adverse events that either start or worsen in severity (measured by CTCAE grade) on or after the date/time of first dose of study treatment.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment.

For the purpose of calculating treatment emergent AEs, incomplete onset dates will be imputed as detailed in [Appendix 6-2](#).

The following summaries will be provided:

- An overview of any AEs, TEAEs including severity, Drug related TEAEs including severity, serious TEAEs, TEAEs leading to withdrawals, TEAEs leading to drug interruption will be presented by treatment group.
- An overview of COVID-19 TEAEs and serious COVID-19 TEAEs will be presented by treatment group.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by treatment group, SOC, and PT
- A summary of the most common treatment-emergent adverse events by treatment group and PT (reported by > 5% of subjects in any treatment group).
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event by treatment group, severity, SOC and PT

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the combined two arms. If the frequency of the PTs were tied, the PTs were ordered alphabetically.

Drug related TEAEs are defined as TEAEs related to any study treatment (afuresertib or Paclitaxel), if causality is missing, the worst case will be assumed.

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. If severity is missing, the worst case will be assumed.

A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided.

A by-subject listing of TEAEs for COVID-19 will be provided by treatment group.

4.10.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Following summaries will be provided for deaths, Serious Adverse Events, and Other Significant Adverse Events:

- A summary of the number and percentage of TEAEs leading to death during the study by treatment group, SOC, and PT.
- A summary of the number and percentage of subjects reporting a serious treatment-emergent adverse event, by treatment group, SOC and PT.
- A summary of the number and percentage of subjects reporting a serious treatment-emergent adverse event, by treatment group, severity, SOC and PT.
- A summary of the number and percentage of subjects with TEAEs leading to discontinuation of study treatment, by treatment group, SOC and PT.
- A summary of the number and percentage of subjects with TEAEs leading to discontinuation of study treatment, by treatment group, severity, SOC and PT.
- A summary of the number and percentage of subjects reporting a drug related adverse event by treatment group, SOC and PT.

- A summary of the number and percentage of subjects reporting a drug related adverse event by treatment group, severity, SOC and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event requiring dose adjustment or interruption by treatment group, SOC, and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent adverse event requiring dose adjustment or interruption by treatment group, severity, SOC, and PT.
- A summary of the number and percentage of subjects reporting a CTCAE grade ≥ 3 treatment-emergent adverse event by treatment group, SOC, and PT.
- A summary of the number and percentage of subjects reporting a CTCAE grade ≥ 3 treatment-emergent adverse event by treatment group, severity, SOC, and PT.

Describe the listings that are to be provided. These may include the following listings:

- A by-subject listing of all AEs leading to deaths that occurred during the study
- A by-subject listing of all serious adverse events
- A by-subject listing of all adverse events leading to discontinuation of study treatment

4.10.4 Clinical Laboratory Evaluation

The following laboratory parameters will be measured:

- Hematology: Platelet Count, Hemoglobin, WBC Count (absolute), Neutrophils Count, Eosinophils Count, Basophils Count, Lymphocytes Count, Monocytes Count
- Coagulation: PT (Prothrombin time), INR, APTT
- Standard Clinical Chemistry: BUN, Urea, Creatinine, Glucose (fasting), Sodium, Total Protein, Magnesium, Potassium, Chloride, Total CO₂, Bicarbonate, Calcium, Albumin, AST (SGOT), ALT (SGPT), Phosphorous, Alkaline phosphatase, Total and direct bilirubin
- Additional Chemistry/Laboratory Assessments: Creatinine clearance, Fasting lipid panel, CA-125, TSH, Insulin, HbA1C and 1,5-anhydroglucitol

All laboratory values will be converted into SI units, for by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each scheduled visit will be summarized. For across visit summaries (e.g., maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

Quantitative laboratory measurements reported as '< X', i.e. below the lower limit of quantification (BLQ), or '> X', i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as '< X' or '> X' in the listings.

The baseline for the laboratory values will be the results obtained on the last measurement before the first dose of the study treatment. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the

clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS).

Laboratory measurements will be graded using the CTCAE v5.0. Abnormal values will be graded in Grade 1 to 5 according the CTCAE criteria in [APPENDIX 6-3](#) and normal values will be presented as Grade 0. In case of overlapped range between local normal range and abnormal criteria in CTCAE grading, local normal range will be considered preferentially.

The following summaries will be provided for the laboratory data for Safety Analysis Set:

- A shift table of the number and percentage of subjects with laboratory AEs by CTCAE Grade at baseline and worst case at post-baseline, for CTCAE v5.0 gradable laboratory parameters, by treatment group
- A shift table of the number and percentage of subjects experiencing low, normal or high values at baseline and worst case at post-baseline scheduled visit, by Hematology, Chemistry, Coagulation parameter and treatment group.
- By-subject listings of laboratory data will be provided by treatment group respectively, including laboratory reference range in SI unit, with indicator of abnormal values (Low/Nomal/High), and CTCAE grade.

4.10.5 Vital Signs, Physical Findings and Other Observations Related to Safety

The results of scheduled assessments of vital signs, physical examinations, and 12-lead electrocardiogram (ECG) will be summarized. Summaries will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied).

4.10.5.1 Vital Signs

Vital signs (Weight, body surface area [BSA], systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, body temperature, respiratory Rate) will be assessed as shown in [Appendix 6-1](#). Systolic BP, diastolic BP, and heart rate will be assessed up to 3 consecutive measurements with a minimal 5 minutes interval in the seated or supine position using a completely automated device, average of the measurements will be used for summary. The following vital signs measurements will be obtained:

- A by-subject listing of vital signs data will be provided.

4.10.5.2 Physical examinations

Physical examinations will be assessed as shown in [Appendix 6-1](#) and summarized as below:

- A shift table to present normal/abnormal physical examination findings change from baseline by body system, treatment group and timepoint.
- A by-subject listing of physical examinations will be provided.

4.10.5.3 12-lead electrocardiogram

12-lead ECG (Including heart rate, PR, QRS, QT, and QTc intervals) will be performed by qualified personnel at screening. The ECG will be evaluated by the Investigator as 'Normal',

‘Abnormal, NCS’ or ‘Abnormal, CS’. QTcF with Frederica’s correction will also be calculated and collected with the formula below:

- The Fridericia’s formula is: $QTcF = QT \times (1/[RR])^{1/3}$

If multiple assessments have been performed at screening, then the last non-missing assessment before first study treatment will be used for summary.

The following summaries of ECG data may be provided:

- A by-subject listing of ECG will be provided.

4.10.6 Safety Monitoring (Safety Review Committee [SRC])

The safety events will be reviewed by a Study Safety Review Committee (SRC) composed of medical and safety representatives from the Sponsor, CRO, and Gynecology Oncology Group Foundation as necessary on a regular basis throughout trial conduct.

4.11 Other Analyses

4.11.1 Pharmacokinetics

4.11.1.1 PK concentration data analysis

Blood sample concentration data analysis is based on the PAS.

A listing of afuresertib and paclitaxel PK collection times and sampling time deviations are provided. Unscheduled or unplanned sample will be presented in this listing. Individual afuresertib and paclitaxel PK concentrations will be listed by scheduled sampling time. For statistical summary of afuresertib and paclitaxel PK concentration data, the data below quantitation limit (BQL) will be set as 0 and presented as "BQL" in the listings. Missing data are treated as missing. PK concentrations of afuresertib and paclitaxel will be summarized by treatment, analyte, and scheduled sampling time, including the number of evaluable cases (n), arithmetic mean, standard deviation (SD), arithmetic %CV, minimum, median, maximum, geometric mean, geometric SD, and geometric CV%.

Mean afuresertib and paclitaxel PK concentration-time profiles (linear and semi-logarithmic) for the intensive serial PK samples (Cycle 1 day 1 and Cycle 2 day 1) will be plotted by treatment, analyte, and scheduled sampling timepoint. Individual afuresertib and paclitaxel PK concentration-time profiles (linear and semi-logarithmic) for the intensive serial PK samples will be plotted by treatment, analyte, and actual sampling timepoint. Mean and individual concentration-time profiles (linear and semi-logarithmic) for the sparse PK samples (pre-dose PK samples) of afuresertib will be plotted by visit. Spaghetti individual plasma concentrations-time plots (linear and semi-logarithmic) in each arm for the intensive serial PK samples (Cycle 1 day 1 and Cycle 2 day 1) and spaghetti individual trough plasma concentrations-time plots (linear and semi-logarithmic) of afuresertib for the sparse PK samples (pre-dose PK samples) will be plotted by actual sampling timepoint.

4.11.1.2 PK parameter analysis

The PK parameter analysis is based on the PK evaluable set.

For PK parameters calculation, noncompartmental analysis (NCA) will be performed by Phoenix WinNonlin v8.0 version or above (Certara, Princeton, New Jersey, United States). The actual sampling time will be used in the calculation of PK parameters. Concentration data which are BQL before the first measurable concentration will be set as 0 and as missing if measured after.

Where applicable, the following PK parameters for afuresertib will be calculated.

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Arm 1: afuresertib First Dose (Cycle 1 Day 1)

Parameter	Definition
AUC_{0-t}	Area under the curve from the time of dosing to the time of the last measurable concentration, calculated by linear up/log down trapezoidal summation.
AUC_{0-24h}	Area under the curve from the time of dosing to 24 h, calculated by linear up/log down trapezoidal summation.
AUC_{0-inf}	AUC from time of dosing extrapolated to infinity, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration (C_t) divided by the apparent terminal rate constant (λ_z): $AUC_{(0-last)} + C_t/\lambda_z$
C_{max}	Maximum observed concentration, obtained from the concentration-time data.
T_{max}	Time of reach C_{max} .
$t_{1/2}$	Terminal half-life.
CL/F	Systemic clearance.
MRT_{last}	Mean residence time extrapolated to infinity.
V_z/F	Volume of distribution based on the terminal phase.
T_{last}	Time of last measurable observed concentration.

Arm 1: afuresertib Multiple Dose (Cycle 2 Day 1)

Parameter	Definition
AUC_{0-tau}	AUC over the dosing interval (dosing interval $\tau = 24$ h), calculated by linear up/log down trapezoidal summation
$C_{max,ss}$	Maximum observed concentration at steady-state
$T_{max,ss}$	Time of maximum observed concentration at steady-state
$C_{min,ss}$	Minimum observed concentration at steady-state
$C_{avg,ss}$	Average concentration at steady-state
$t_{1/2}$	Terminal half-life
CL_{ss}/F	Systemic clearance at steady-state
MRT_{last}	Mean residence time (MRT) extrapolated to infinity
$V_{z,ss}/F$	Volume of distribution based on the terminal phase
$R_{ac}(AUC)$	Accumulation ratio of AUC ($AUC_{0-tau} / AUC_{0-24h}$)
$R_{ac}(C_{max})$	Accumulation ratio of C_{max} ($C_{max,ss} / C_{max}$)

Where applicable, the following PK parameters for paclitaxel will be calculated.

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Arm 1: paclitaxel First Dose (Cycle 1 Day 1)

Parameter	Definition
AUC_{0-t}	Area under the curve from the time of dosing to the time of the last measurable concentration, calculated by linear up/log down trapezoidal summation.
AUC_{0-inf}	AUC from time of dosing extrapolated to infinity, calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration (C_t) divided by the apparent terminal rate constant (λ_z): $AUC_{(0-last)} + C_t/\lambda_z$
C_{max}	Maximum observed concentration, obtained from the concentration-time data.
T_{max}	Time of reach C_{max} .
$t_{1/2}$	Terminal half-life.
CL	Systemic clearance.
MRT_{last}	Mean residence time extrapolated to infinity.
V_z	Volume of distribution based on the terminal phase.
T_{last}	Time of last measurable observed concentration.

Arm 1: paclitaxel Multiple Dose (Cycle 2 Day 1)

Parameter	Definition
$AUC_{0-t,ss}$	Area under the curve from the time of dosing to the time of the last measurable concentration at multiple dose, calculated by linear up/log down trapezoidal summation.
AUC_{0-tau}	AUC over the dosing interval (dosing interval $\tau = 168$ h), calculated by linear up/log down trapezoidal summation
$C_{max,ss}$	Maximum observed concentration at steady-state
$T_{max,ss}$	Time of maximum observed concentration at steady-state
$C_{min,ss}$	Minimum observed concentration at steady-state
$t_{1/2}$	Terminal half-life
CL_{ss}	Systemic clearance at steady-state
MRT_{last}	Mean residence time (MRT) extrapolated to infinity
$V_{z,ss}$	Volume of distribution based on the terminal phase
V_{ss}	Volume of distribution at steady-state
$R_{ac}(AUC)$	Accumulation ratio of AUC ($AUC_{0-t,ss} / AUC_{0-t}$)
$R_{ac}(C_{max})$	Accumulation ratio of C_{max} ($C_{max,ss} / C_{max}$)
T_{last}	Time of last measurable observed concentration at steady-state

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Arm 2: paclitaxel Multiple Dose (Cycle 2 Day 1)

Parameter	Definition
$AUC_{0-t,ss}$	Area under the curve from the time of dosing to the time of the last measurable concentration at multiple dose, calculated by linear up/log down trapezoidal summation.
$AUC_{0-\tau}$	AUC over the dosing interval (dosing interval $\tau = 168$ h), calculated by linear up/log down trapezoidal summation
$C_{max,ss}$	Maximum observed concentration at steady-state
$T_{max,ss}$	Time of maximum observed concentration at steady-state
$C_{min,ss}$	Minimum observed concentration at steady-state
$t_{1/2}$	Terminal half-life
CL_{ss}	Systemic clearance at steady-state
MRT_{last}	Mean residence time (MRT) extrapolated to infinity
$V_{z,ss}$	Volume of distribution based on the terminal phase
V_{ss}	Volume of distribution at steady-state
T_{last}	Time of last measurable observed concentration at steady-state

The following PK parameters will be calculated for diagnostic purposes, where applicable, and will be listed, but will not be summarized:

- λ_z
- The time interval (h) of the log-linear regression used to determine λ_z (λ_{z_lower} and λ_{z_upper});
- Number of data points included in the log-linear regression analysis (N_{pt});
- Coefficient of determination (R_{sq}) for calculation of λ_z . The λ_z and related parameters will be considered reliable only if R_{sq} is ≥ 0.800 . A minimum of 3 data points will be used for λ_z determination; and
- Percentage of AUC_{0-inf} obtained by extrapolation ($\%AUC_{ex}$). If $\%AUC_{ex}$ is greater than 30%, then AUC_{0-inf} will be considered as unreliable and PK parameters AUC_{0-inf} , $t_{1/2}$, CL , CL_{ss} , CL/F , CL_{ss}/F , V_z , $V_{z,ss}$, V_z/F , $V_{z,ss}/F$, and V_{ss} will not be included in the statistical summary.

All PK parameters except T_{max} will be summarized by descriptive statistics, including n, arithmetic mean, SD, minimum, median, maximum, arithmetic %CV, geometric mean, geometric SD, and geometric CV%. For T_{max} , only n, minimum, median, and maximum will be reported.

4.11.1.3 PK Reporting Rules

For PK concentration and parameter data, a minimum of $n=3$ is required for all descriptive statistics to be generated. If n is less than 3, only n , minimum, and maximum will be reported.

All raw PK data will be reported and analyzed with the same precision as the source regardless of how many significant figures or decimals the data carry. Derived PK data will be rounded for reporting purposes both in the summary tables and by subject listings. For the calculation of

descriptive statistics, rounded values as presented in the data listings will be used. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (include $C_{\max}$, $C_{\max,SS}$, and $C_{\min,SS}$) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual sample collection times ($T_{\max}$ and $T_{\max,SS}$) will be reported to 2 decimal place.

Reporting of mean, SD, minimum, median, maximum, geometric mean, and geometric SD will follow the rounding convention of the individual PK data. CV% and geometric CV% (expressed as a percentage) will always be reported to 1 decimal place.

Some minor modifications may be necessary to the planned design of tables, listings, and figures to accommodate data collected during the actual study conduct.

4.11.1.4 Population PK Analysis

Population PK analysis plan and report will be described in separate documents.

4.11.2 Biomarkers

Subgroup analyses will be performed for PFS, OS, ORR, BOR, DOR, DCR based on RECIST 1.1, and CA-125 response (GCIG), to evaluate the efficacy of afuresertib administered in combination with paclitaxel versus paclitaxel which includes but not limited to following subgroups:

- PI3K/AKT/PTEN pathway alterations by NGS (no versus yes)
- BRCA mutations by NGS (no versus yes)
- Levels of phospho-AKT in tumor sample as assessed by immunohistochemistry (IHC) (positive versus negative)

The subgroup analyses will be based on the values preformed at a central vendor as indicated above.

For PFS and OS, the median survival time will be estimated by Kaplan-Meier method for each subgroup. The hazard ratio (afuresertib administered in combination with paclitaxel versus paclitaxel) and 95% CI will be estimated by an unstratified Cox proportional hazards model with treatment as only fixed effect. Efron's method will be used to handle ties. A Forest plot, along with the results of the overall analysis will be produced for subgroups, using FAS.

For subgroup analyses of ORR, DCR, and CA-125 response, the efficacy analysis methods in Section 4.9.3 will be used as appropriate.

4.12 Determination of Sample Size

The primary endpoint of this study is PFS. Previous studies have shown that PROC patients have a median PFS of around 3.5 months with weekly paclitaxel after 1 to 5 prior platinum-based chemotherapies before PROC was diagnosed. The combination therapy is expected to result in an improved median PFS, i.e. 6.5 months, corresponding to a 46% reduction of the disease

progression risk. Patients will be randomized in a 2:1 ratio to the combination and monotherapy arms. With the two-sided type I error rate controlled at 0.05, a total of 105 events are needed to provide about 85% statistical power to test the difference between the 2 therapies.

Consider a censoring rate of 25%, a total number of 141 subjects (94 patients in the combination treatment arm and 47 patients in the monotherapy arm) will be enrolled and randomized to observe 105 events.

The primary statistical analysis will be based on the unstratified log-rank test. The hazard ratio and 95% CI will be calculated based on an unstratified Cox proportional hazards model. Stratified analysis results will be provided to check robustness of the primary results.

4.13 Changes in the Conduct of the Study or Planned Analysis

- It was decided by sponsor that the subgroup analysis for DOR was removed from the scope of this SAP, which is different with protocol section 10.3.3.3.6 Predictive Biomarker Analyses.
- It was decided by sponsor that the minimum interval of SD criteria was changed from “after first dose at a minimum interval of 42 days” to “after randomization at a minimum interval of 42 days”, which is different with protocol section 8.3.4.4.5 Evaluation of Best Overall Response.

5 REFERENCES

[1] Eisenhauer, E.A., et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2): p. 228-47.

[2] Rustin GJS, Vergote I, Eisenhauer E et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA-125 agreed by the Gynecological Cancer Intergroup (GCIC). Int J Gynecol Cancer. 2011; 21(2):419-423.

6 Appendix

6.1 Appendix 6-1. Time and Events Table

For patients in both Arm 1 (afuresertib QD + paclitaxel once weekly [QW], 3 weeks is a cycle) and Arm 2 (paclitaxel QW, 3 weeks is a cycle):

	Screening ²	Cycle 1			Cycle 2			Subsequent Cycles			End of Treatment ³	OS Follow-Up
	Day -24 to -1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Within 30 days (±7 days) of last dose	Every 12 weeks (±7 days)
Procedure¹												
Informed consent	X											
Inclusion/exclusion criteria	X											
Baseline demographics	X											
Medical history	X											
Physical exam ⁴	X	X ⁷		X		X		X			X	
ECOG performance status	X	X ⁷									X	
Vital signs ^{4,5}	X	X ⁷		X		X		X			X	
Weight and height ⁶	X	X ⁷		X		X		X			X	
CBC ⁸ (Hematology)	X	X ⁷	X	X	X	X	X	X			X	
Clinical chemistry	X	X ⁷			X			X			X	

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	Screening ²	Cycle 1			Cycle 2			Subsequent Cycles			End of Treatment ³	OS Follow-Up
	Day -24 to -1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Within 30 days (±7 days) of last dose	Every 12 weeks (±7 days)
Procedure¹												
Coagulation	X				X			Weeks 13 and 28 and then every 12 weeks ⁹				
Creatinine clearance ¹⁰	X				X			Weeks 13 and 28 and then every 12 weeks ⁹				
Serology (HBV, HCV, HIV) and TB	X											
Pregnancy test ¹¹	X							Weeks 13 and 28 and then every 12 weeks ⁹				
Fasting lipid panel, hemoglobin A1C, TSH	X							Weeks 13 and 28 and then every 12 weeks ⁹				
1,5-anhydroglucitol and insulin ¹²	X				X			Week 7 and 12, then every 12 weeks ⁹				

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Procedure ¹	Screening ²	Cycle 1			Cycle 2			Subsequent Cycles			End of Treatment ³	OS Follow-Up
	Day -24 to -1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Within 30 days (±7 days) of last dose	Every 12 weeks (±7 days)
CA-125 ^{1,13}	X							Every 6 weeks × 30 weeks, then every 8 weeks ⁹			X ²⁰	
12-lead ECG	X											
Randomization		X ²⁴										
Fingerstick blood glucose		At home daily during first 3 weeks of therapy			As clinically needed							
Pharmacokinetics ¹⁴		X ¹⁵			X ¹⁵			X ¹⁵				
Fresh tumor biopsy ¹⁶	X											
Archival tumor biopsy ¹⁷	X											
Paclitaxel (IV) dosing (Arm 1 and Arm 2) ¹⁸		X	X	X	X	X	X	X	X	X		
Afuresertib dosing ¹⁹		X	Continuous QD dosing									
Tumor assessment ¹	X							Every 6 weeks × 30 weeks, then every 8 weeks ⁹			X ²⁰	
Survival contact												X
Diary ²¹												

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Procedure ¹	Screening ²	Cycle 1			Cycle 2			Subsequent Cycles			End of Treatment ³	OS Follow-Up
	Day -24 to -1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±1 day)	Day 8 (±1 day)	Day 15 (±1 day)	Within 30 days (±7 days) of last dose	Every 12 weeks (±7 days)
Concomitant medication	X	X ²²										
Adverse events	X	X ²³										

Notes:

- For post-baseline assessments, a window of ± 1 day is permitted to allow for flexible scheduling in all cycles; however, a window of ± 7 days is permitted for post-baseline tumor assessments and CA-125 measurements. A window of ± 7 days is permitted for the EOT and OS follow-up.
- All screening assessments must be completed within 24 days prior to the first dose, except tumor assessments, which can occur within 28 days prior to the first dose.
- The End-of-Treatment visit should be within 30 days (± 7 days) from the last dose of study drug. If a patient is unable to return to the clinic due to hospitalization, site staff are encouraged to contact the patient for assessment of concomitant medications and AEs or SAEs. Note: for patients that have not progressed or died see [Section Error! Reference source not found. of protocol](#).
- This assessment to be completed every 2 weeks for the first 2 cycles, then once per cycle.
- Resting vital signs assessed will include systolic and diastolic blood pressure (BP), heart rate, respiratory rate, and temperature, taken in a seated or supine position.
- Height at screening only.
- If within 96 hours of Day 1, this assessment does not need to be repeated on Day 1.
- CBC to be tested every week for the first 2 cycles, then once per cycle (ie, once every 3 weeks).
- These assessments are calendar-based.
- Creatinine clearance calculated using the Cockcroft-Gault formula.
- Pregnancy testing in women of childbearing potential: serum human chorionic gonadotropin (hCG) should be tested at screening. Serum or urine may be performed through the duration on study.
- The timing of 1,5-anhydroglucitol and insulin assessments may be altered so that they coincide with PK assessments to facilitate any potential PK tests.
- If maintaining the timing of the CA-125 assessment as indicated requires a clinic visit in which this is the ONLY assessment being done, then the timing of the assessment can be adjusted so that it is done at the next scheduled clinic visit. CA-125 measurement will have the same frequency as tumor assessment, but additional tests can be done when requested by the treating physician until End of Treatment.

14. The timing of the PK time points may be altered so that they coincide with paclitaxel dosing; eg, if paclitaxel dosing is delayed, then the PK sample should be delayed by the same duration.
15. PK sampling time points are described below (see [protocol Section Error! Reference source not found.](#) and 8.4.1 for further details). “Pre-dose” refers to before the administration of either agent in combination treatment. “Post-dose” refers to a time point after the start of infusion of paclitaxel.
 - From approximately 20 patients in Arm 1 and 10 patients in Arm 2, multiple blood samples will be taken according to the scheme as follows:
 - Arm 1:
 - Cycle 1 Day 1: pre-dose and at 1 (at the end of paclitaxel infusion), 2, 3, 4, 8 and 24 hours post-dose.
 - Cycle 2 Day 1: pre-dose and at 0.5, 1 (at the end of paclitaxel infusion), 2, 3, 4, 8, and 24 hours post-dose.
 - Arm 2:
 - Cycle 2 Day 1: pre-dose and at 0.5, 1 (at the end of paclitaxel infusion), 2, 3, 4, 8, and 24 hours post-dose.
 - Pre-dose PK sample should be collected before administration of either study drug and preferably within 2 hours before afuresertib is administered. Afuresertib should be administered orally within 15 minutes of the starting time of paclitaxel IV infusion (time zero). Post-dose refers to timepoints after the start of the paclitaxel infusion. The 24-hour timepoints are pre-dose of Day 2 of the corresponding cycle. Each post-dose PK sample should be collected within $\pm 10\%$ time window of the planned timepoints in reference to the starting time of paclitaxel IV infusion on serial PK days. Note: On PK sample collection days, efforts should be made to complete the infusion in 1 hour ± 6 minutes. If the paclitaxel infusion time is prolonged (> 1 hour ± 6 minutes) due to infusion reaction, the 1-hour post-dose PK sample should be collected immediately at the end of the infusion.
 - For all patients in Arm 1, $C_{trough,SS}$ PK samples for afuresertib will be obtained pre-dose on Cycle 3 Day 1 and Cycle 4 Day 1.
16. Fresh tumor biopsy is optional. This tumor sample will be used for testing only for the patients who could not provide at least 15 slides of tumor tissue samples from previous archival tumor sample for both tests. If patients had archival tumor samples from less than 1 year before the screening visit, the fresh biopsy can be waived.
17. Archival tumor tissue collected within 1 year before the screening visit is preferred, but older samples are acceptable.
18. Frequent vital sign monitoring is required after administration of paclitaxel.
19. All patients in Arm 1 will receive daily afuresertib together with the planned chemotherapy.
20. Follow-up disease assessment and CA-125 measurement required for patients who discontinue study drug for any reason other than disease progression, death or withdrawal of consent for further treatment and data collection.
21. Patient must record in a diary each day: study drug dosing, AEs, concomitant medication dosing, and glucose level (fingerstick). Patients should bring the diary to each visit for site review.
22. Post-discontinuation treatment and treatment outcome should be collected.
23. All AE will be reported from ICF until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice. During the OS period, the investigator may report any AE that he/she believes is related to study treatment.
24. Randomization could be performed up to 4 days prior to C1D1 (Day -4 to Day 1 of Cycle 1).

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AE = Adverse event; BP = Blood pressure; CA-125 = Cancer antigen-125; CBC = Complete blood count; ECG = Electrocardiogram;
ECOG = Eastern Cooperative Oncology Group; HBV = Hepatitis B virus; hCG = Human chorionic gonadotropin; HCV = Hepatitis C virus;
HIV = Human immunodeficiency virus; IHC = Immunohistochemistry; IV = Intravenous; OS = Overall survival; PK = Pharmacokinetic;
PTEN = Phosphatase and tensin analog protein; QD = Once daily; QW = Once weekly; SAE = Serious adverse event; TB: tuberculosis;
TSH = Thyroid stimulating hormone.

6.2 Appendix 6-2: Imputation algorithm for partial and missing dates

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to the date of first dose of trial medication.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dosing, then set month and day to month and day of first dosing
- If year < year of first dosing, then set month and day to December 31.
- If year > year of first dosing, then set month and day to January 1.

If month and year are present and day is missing:

- If year=year of first dosing and
 - If month = month of first dosing then set day to day of first dose
 - If month < month of first dose then set day to last day of month
 - If month > month of first dose then set day to first day of month
- If year < year of first dosing then set day to last day of month
- If year > year of dosing then set day to first day of month

For all other cases, set onset date to date of first dosing.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to first dosing, then the medication will be classified as concomitant if there is no other evidence to indicate medication start before first study treatment, or classified as prior and concomitant if there is other evidence to indicate medication start before first study treatment. If start date is completely missing and end date is prior to first dosing, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant, or prior and concomitant if there is evidence to indicate medication start before first study treatment. If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing, then the medication will be classified as concomitant only once there is no other evidence to indicate medication start before first study

treatment, and classified as prior and concomitant if there is evidence to indicate medication start before first study treatment.

For Death

Suppose death year and month (yyyymm) are available but day is missing:

- If yyyymm for death date = yyyymm for last known alive date, then set day to the day after the last known alive date;
- If yyyymm for death date > yyyymm for last known alive date, then set day to the first day of the month;
- If yyyymm for death date < yyyymm for last known alive date, data error and do not impute.

If both month and day are missing for death date or death date is totally missing, do not impute and censor the subject at the last known alive date.

6.3 Appendix 6-3: CTCAE 5.0 for Selected Laboratory Parameters

Parameter	Direction	Standard Unit	1	2	3	4	5
Hemoglobin	Hypo	g/L	$100 \leq \text{Value} < \text{LLN}$	$80 \leq \text{Value} < 100$	Value < 80	-	-
	Hyper	g/L	$\text{ULN} < \text{Value} \leq \text{ULN} + 20$	$\text{ULN} + 20 < \text{Value} \leq \text{ULN} + 40$	$\text{ULN} + 40 < \text{Value}$	-	-
Platelet count	Hypo	$10^9/\text{L}$	$75 \leq \text{Value} < \text{LLN}$	$50 \leq \text{Value} < 75$	$25 \leq \text{Value} < 50$	Value < 25	-
White blood cell	Hypo	$10^9/\text{L}$	$3 \leq \text{Value} < \text{LLN}$	$2 \leq \text{Value} < 3$	$1 \leq \text{Value} < 2$	Value < 1	-
	Hyper	$10^9/\text{L}$	-	-	$100 < \text{Value}$	-	Death
Absolute Eosinophils count	Hyper	$10^9/\text{L}$	>ULN and >Baseline	-	Steroids initiated	-	-
Absolute neutrophil count	Hypo	$10^9/\text{L}$	$1.5 \leq \text{Value} < \text{LLN}$	$1 \leq \text{Value} < 1.5$	$0.5 \leq \text{Value} < 1$	Value < 0.5	-
Absolute lymphocyte count	Hypo	$10^9/\text{L}$	$0.8 \leq \text{Value} < \text{LLN}$	$0.5 \leq \text{Value} < 0.8$	$0.2 \leq \text{Value} < 0.5$	Value < 0.2	-
	Hyper	$10^9/\text{L}$	-	$4 < \text{Value} \leq 20$	$20 < \text{Value}$	-	-
Sodium	Hypo	mmol/L	$130 \leq \text{Value} < \text{LLN}$	$125 \leq \text{Value} \leq 129$ and asymptomatic	$125 \leq \text{Value} \leq 129$ symptomatic; $120 \leq \text{Value} \leq 124$ regardless of symptoms	Value < 120	Death
	Hyper	mmol/L	$\text{ULN} < \text{Value} \leq 150$	$150 < \text{Value} \leq 155$	$155 < \text{Value} \leq 160$	$160 < \text{Value}$	Death
Potassium	Hypo	mmol/L	$3 \leq \text{Value} < \text{LLN}$	Symptomatic with $3 \leq \text{Value} < \text{LLN}$	$2.5 \leq \text{Value} < 3$	Value < 2.5	Death
	Hyper	mmol/L	$\text{ULN} < \text{Value} \leq 5.5$	$5.5 < \text{Value} \leq 6$	$6 < \text{Value} \leq 7$	$7 < \text{Value}$	Death
Magnesium	Hypo	mmol/L	$0.5 \leq \text{Value} < \text{LLN}$	$0.4 \leq \text{Value} < 0.5$	$0.3 \leq \text{Value} < 0.4$	Value < 0.3	Death
	Hyper	mmol/L	$\text{ULN} < \text{Value} \leq 1.23$	-	$1.23 < \text{Value} \leq 3.3$	$3.3 < \text{Value}$	Death
Creatinine	Hyper	umol/L	$\text{ULN} < \text{Value} \leq 1.5 \times \text{ULN}$	$1.5 \times \text{ULN} < \text{Value} \leq 3 \times \text{ULN}$; Or $1.5 \times \text{BL} < \text{Value} \leq 3 \times \text{BL}$	$3 \times \text{ULN} < \text{Value} \leq 6 \times \text{ULN}$; or $3 \times \text{BL} < \text{Value}$	$6 \times \text{ULN} < \text{Value}$	-
Blood glucose	Hypo	mmol/L	$3 \leq \text{Value} < \text{LLN}$	$2.2 \leq \text{Value} < 3$	$1.7 \leq \text{Value} < 2.2$	Value < 1.7	Death

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Parameter	Direction	Standard Unit	1	2	3	4	5
Aspartate aminotransferase (AST)	Hyper	U/L	ULN < Value ≤ 3 × ULN, if BL is normal	3 × ULN < Value ≤ 5 × ULN, if BL is normal	5 × ULN < Value ≤ 20 × ULN, if BL is normal	20 × ULN < Value, if BL is normal	-
			1.5 × BL ≤ Value ≤ 3.0 × BL, if BL is abnormal	3.0 × BL < Value ≤ 5.0 × BL, if BL is abnormal	5.0 × BL < Value ≤ 20.0 × BL, if BL is abnormal	20.0 × BL < Value, if BL is abnormal	-
Alanine aminotransferase (ALT)	Hyper	U/L	ULN < Value ≤ 3 × ULN, if BL is normal	3 × ULN < Value ≤ 5 × ULN, if BL is normal	5 × ULN < Value ≤ 20 × ULN, if BL is normal	20 × ULN < Value, if BL is normal	-
			1.5 × BL ≤ Value ≤ 3.0 × BL, if BL is abnormal	3.0 × BL < Value ≤ 5.0 × BL, if BL is abnormal	5.0 × BL < Value ≤ 20.0 × BL, if BL is abnormal	20.0 × BL < Value, if BL is abnormal	-
Alkaline phosphatase (ALP)	Hyper	U/L	ULN < Value ≤ 2.5 × ULN, if BL is normal	2.5 × ULN < Value ≤ 5.0 × ULN, if BL is normal	5.0 × ULN < Value ≤ 20.0 × ULN, if BL is normal	20.0 × ULN < Value, if BL is normal	-
			2.0 × BL ≤ Value ≤ 2.5 × BL, if BL is abnormal	2.5 × BL < Value ≤ 5.0 × BL, if BL is abnormal	5.0 × BL < Value ≤ 20.0 × BL, if BL is abnormal	20.0 × BL < Value, if BL is abnormal	-
Calcium (Corrected serum)	Hypo	mmol/L	2 ≤ Value < LLN	1.75 ≤ Value < 2	1.5 ≤ Value < 1.75	Value < 1.5	Death
	Hyper	mmol/L	ULN < Value ≤ 2.9	2.9 < Value ≤ 3.1	3.1 < Value ≤ 3.4	3.4 < Value	Death
Albumin	Hypo	g/L	30 ≤ Value < LLN	20 ≤ Value < 30	Value < 20	Life-threatening consequences; urgent intervention indicated	Death
Total bilirubin	Hyper	umol/L	ULN < Value ≤ 1.5 × ULN, if baseline is normal	1.5 × ULN < Value ≤ 3 × ULN, if baseline is normal	3.0 × ULN < Value ≤ 10 × ULN, if baseline is normal	10 × ULN < Value, if baseline is normal	-
			1.0 × BL < Value ≤ 1.5 × BL, if BL is abnormal	1.5 × BL < Value ≤ 3.0 × BL, if BL is abnormal	3.0 × BL < Value ≤ 10.0 × BL, if BL is abnormal	10.0 × BL < Value, if BL is abnormal	-
Activated partial thromboplastin time (APTT) prolonged	Hyper		ULN < Value ≤ 1.5 × ULN	1.5 x ULN < Value ≤ 2.5 x ULN	2.5 x ULN < Value	-	-

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Parameter	Direction	Standard Unit	1	2	3	4	5
International normalized ratio (INR)	Hyper		$1.2 < \text{Value} \leq 1.5$	$1.5 < \text{Value} \leq 2.5$	$2.5 < \text{Value}$	-	-
Triglycerides	Hyper	mmol/L	$1.71 \leq \text{Value} \leq 3.42$	$3.42 < \text{Value} \leq 5.7$	$5.7 < \text{Value} \leq 11.4$	>11.4	Death
Cholesterol	Hyper	mmol/L	$\text{ULN} < \text{Value} \leq 7.75$	$7.75 < \text{Value} \leq 10.34$	$10.34 < \text{Value} \leq 12.92$	>12.92	-

BL = Baseline, LLN = Lower limit of normal range, ULN = Upper limit of normal range.

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